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Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

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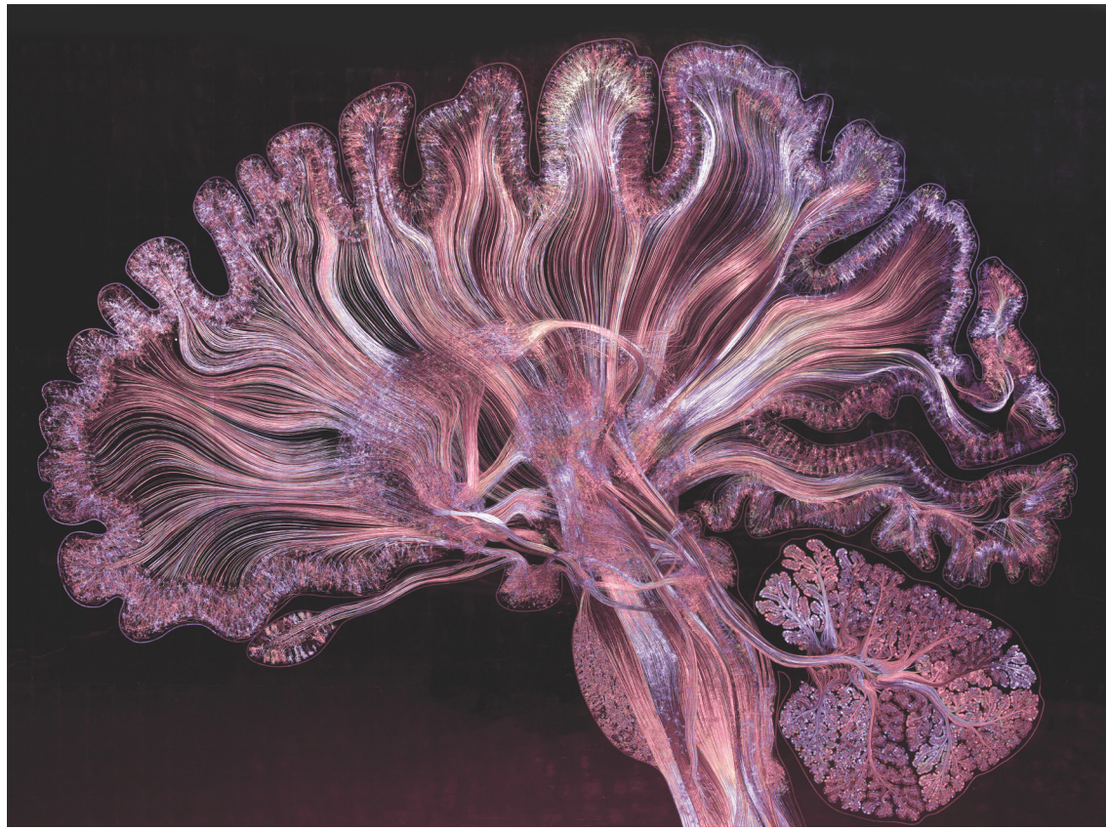

Bárbara Avelar Pereira

Karolinska Institutet

From the Aging Research Center, Department of Neurobiology, Care Sciences, and Society,
Karolinska Institutet, Stockholm, Sweden

MULTIMODAL IMAGING: FUNCTIONAL, STRUCTURAL, AND MOLECULAR BRAIN CORRELATES OF COGNITIVE AGING

Bárbara Avelar Pereira

Karolinska Institutet

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Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

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By

Bárbara Avelar Pereira

Principal Supervisor:

Professor Lars Bäckman
Karolinska Institutet
Department of Neurobiology,
Care Sciences, and Society
Aging Research Center

Co-supervisors:

Assistant Professor Alireza Salami
Karolinska Institutet
Department of Neurobiology,
Care Sciences, and Society
Aging Research Center

and

Umeå University
Umeå Center for Functional Brain Imaging
Department of Radiation Sciences
Department of Integrative Medical Biology

Professor Lars Nyberg
Umeå University
Umeå Center for Functional Brain Imaging
Department of Radiation Sciences
Department of Integrative Medical Biology

Opponent:

Assistant Professor Gagan Wig
University of Texas at Dallas
School of Behavioral and Brain Sciences
Center for Vital Longevity

Examination Board:

Professor Fredrik Ullén
Karolinska Institutet
Department of Neuroscience

Associate Professor Johan Lundström
Karolinska Institutet
Department of Clinical Neuroscience

and

Stockholm University
Stockholm University Brain Imaging Centre

Associate Professor Michael Schöll
University of Gothenburg
Department of Psychiatry and Neurochemistry
Wallenberg Centre for Molecular and
Translational Medicine

To my parents

ABSTRACT (ENGLISH)

Aging is associated with a decline in many (but not all) cognitive abilities. Although it remains largely unknown how changes in brain integrity relate to cognitive deficits, these changes are likely expressed across interrelated functional, structural, and molecular layers. This complexity calls for a multimodal imaging approach in age-related mind-brain research. Hence, in this thesis, different imaging modalities were combined in order to study the neural basis of cognitive aging.

Study I investigated functional connectivity patterns among three large-scale functional brain networks (i.e., default mode [DMN], frontoparietal control [FPN], and dorsal attention [DAN] networks) during rest and task in younger and older adults. The FPN was flexible in its affiliation to other networks, given that it was more functionally connected to the DMN during rest and to the DAN during task performance. Age-related differences were stable across states for the FPN, but were only present for connectivity between the DMN and DAN during the task. Taken together, these results suggest that resting-state is not sufficient to uncover the entire functional connectome of the human brain.

Study II identified brain iron as a potential source of age-related differences in connectivity. Greater striatal iron content was associated with lower intrinsic functional connectivity of the caudate and putamen. Additionally, more iron was associated with less connectivity between the putamen and the rest of the brain. Functional connectivity within the putamen was also linked to motor ability, indicating that iron-related connectivity features are behaviorally meaningful.

Study III explored the relationship between functional and structural connectivity, and showed that increased homotopic functional connectivity in the prefrontal cortex was associated with worse microstructural degeneration of the corpus callosum, and exacerbated working memory decline. However, given that the association between function and structure was weak, results also suggest that homotopic functional connectivity can be resilient to change in the integrity of its structural paths.

Study IV found that dopamine and iron in the putamen were positively associated, but only up until middle age. Together with the fact that dopamine requires iron for its synthesis, these results indicate that, for individuals without excessive iron accumulation, more iron is associated with higher dopaminergic activity. Higher iron load in the putamen was also linked to better processing speed for those in middle age.

Collectively, the studies show that functional connectivity is influenced by mental state, white-matter changes, and molecular properties, with the latter also being interrelated among themselves. These different features are associated with performance and interact with each other, suggesting that cognitive decline is linked to a multitude of changes in brain integrity, and that age-related alterations in the human brain are complex and multifaceted.

RESUMO (PORTUGUESE)

O envelhecimento está associado a um declínio em variadas funções cognitivas (mas não em todas). Embora permaneça desconhecido como as alterações na integridade do cérebro se relacionam com défices cognitivos, muito provavelmente, estas expressam-se em camadas funcionais, estruturais, e moleculares que se inter-relacionam. Esta complexidade exige uma abordagem multimodal no estudo da mente e do cérebro, face ao envelhecimento. Como tal, nesta tese, diferentes modalidades de neuroimagiologia foram combinadas para investigar as bases neuronais do envelhecimento cognitivo.

O **estudo I** investigou padrões de conectividade funcional em três networks funcionais de grande escala no cérebro (i.e., default mode [DMN], frontoparietal control [FPN], e a dorsal attention [DAN] network), em jovens e idosos, durante o estado de repouso e durante uma tarefa cognitiva. A FPN foi flexível na sua afiliação a outras networks, por estar mais funcionalmente ligada à DMN em repouso e à DAN durante o desempenho de uma tarefa cognitiva. Diferenças associadas à idade foram estáveis para a FPN em ambos os estados, mas para conectividade entre a DMN e DAN, estas diferenças estiveram presentes apenas durante a tarefa. Em conjunto, os resultados sugerem que a ressonância magnética em estado de repouso não é suficiente para descrever todo o conectoma funcional do cérebro humano.

O **estudo II** identificou ferro no cérebro como uma potencial fonte de diferenças em conectividade ligadas à idade. Mais ferro no corpo estriado estava associado a menor conectividade funcional intrínsica no núcleo caudado e no putamen. Além disso, mais ferro estava ligado a menos conectividade entre o putamen e o resto do cérebro. A conectividade funcional do putamen estava associada à capacidade motora, o que indica que características de conectividade ligadas ao ferro são importantes a nível comportamental.

O **estudo III** explorou a relação entre conectividade funcional e estrutural, revelando que o aumento de conectividade funcional homotópica no córtex pré-frontal estava associado a uma pior degeneração microestrutural do corpo caloso e a um maior declínio em memória de trabalho. Contudo, dado que a associação entre função e estrutura foi fraca, os resultados também sugerem que a conectividade funcional homotópica pode ser resiliente a mudanças na integridade das suas ligações estruturais.

O **estudo IV** demonstrou que a dopamina e o ferro no putamen estavam positivamente associados, mas apenas até à meia-idade. Juntamente com o facto de a dopamina requerer ferro para a sua síntese, estes resultados indicam que, para indivíduos sem acumulação excessiva de ferro no cérebro, mais ferro está relacionado a uma maior atividade dopaminérgica. Mais ferro também estava ligado a melhor velocidade de processamento.

No seu conjunto, os estudos demostram que a conectividade funcional é influenciada pelo estado mental, por alterações em matéria branca, e propriedades moleculares – sendo que as últimas também estão inter-relacionadas. Estas diferentes características estão ligadas ao desempenho cognitivo e interagem entre si; o que sugere que o declínio cognitivo está associado a uma multiplicidade de alterações na integridade do cérebro humano e que estas são complexas e multifacetadas.

SAMENVATTING (DUTCH)

Veroudering is geassocieerd met een afname van veel (maar niet alle) cognitieve vaardigheden. Hoewel het nog grotendeels onbekend blijft hoe veranderingen in de hersenen verband houden met cognitieve tekortkomingen, zijn deze veranderingen waarschijnlijk te vinden in onderling samenhangende functionele, structurele en moleculaire lagen. Deze complexiteit vraagt om een multimodale benadering in hersenonderzoek met betrekking tot veroudering. Daarom werden in dit proefschrift verschillende *imaging*-modaliteiten gecombineerd om de neurale basis van cognitieve veroudering te bestuderen.

Studie I onderzocht functionele verbindingen tussen drie grootschalige functionele hersennetwerken (d.w.z. default mode [DMN], frontoparietale controle [FPN], en dorsale aandachts [DAN] netwerken) tijdens rust en tijdens een taak in jongere en oudere volwassenen. Het FPN had een flexibele connectie met de andere netwerken, gezien het meer functioneel verbonden was met het DMN tijdens rust, en meer met de DAN tijdens taakuitvoering. Leeftijdsgerelateerde verschillen waren stabiel tussen staten voor het FPN, maar waren voor de connectie tussen het DMN en DAN alleen aanwezig tijdens de taak. Samengevat suggereren deze resultaten dat metingen tijdens rust niet voldoende zijn om het gehele functionele connectoom van het menselijk brein te vast te leggen.

Studie II identificeerde ijzer in de hersenen als een potentiele bron van leeftijdsgerelateerde verschillen in connectiviteit. Een hoger striataal ijzergehalte werd geassocieerd met lagere intrinsieke functionele connectiviteit tussen de caudatus en het putamen. Bovendien was meer ijzer geassocieerd met minder connectiviteit tussen het putamen en de rest van de hersenen. Connectiviteit binnen het putamen was ook gekoppeld aan motorische vaardigheden, wat aangeeft dat ijzer-gerelateerde connectiviteitskenmerken relevant zijn voor gedrag.

Studie III onderzocht de relatie tussen functionele en structurele connectiviteit en toonde aan dat verhoogde homotopische functionele connectiviteit in de prefrontale cortex werd geassocieerd met grotere microstructurele degeneratie van het corpus callosum en sterkere achteruitgang van het werkgeheugen. Gegeven dat de associatie tussen functie en structuur zwak was, suggereren de resultaten ook dat homotopische functionele connectiviteit veerkrachtig kan zijn wanneer de integriteit van haar structurele paden verandert.

Studie IV wees uit dat dopamine en ijzer in het putamen positief met elkaar geassocieerd waren, maar alleen tot de middelbare leeftijd. Samen met het feit dat ijzer nodig is voor de synthese van dopamine, geven deze resultaten aan dat, voor personen zonder overmatige ijzeraccumulatie, meer ijzer geassocieerd is met hogere dopaminerge activiteit. Hogere ijzerbelasting in het putamen was ook gekoppeld aan een betere verwerkingssnelheid.

Gezamenlijk tonen de studies aan dat functionele connectiviteit wordt beïnvloed door mentale toestand, veranderingen in witte stof, en moleculaire eigenschappen, waarbij deze laatste onderling ook verbonden zijn. Deze verschillende functies worden geassocieerd met cognitieve prestaties en werken op elkaar in, wat suggereert dat cognitieve achteruitgang samen gaat met een veelheid aan veranderingen in hersenintegriteit en dat leeftijdsgebonden veranderingen in het menselijk brein complex en veelzijdig zijn.

SAMMANFATTNING (SWEDISH)

Åldrande är associerat med en försämring i många (men inte alla) kognitiva förmågor. Även om det är mestadels okänt hur förändringar i hjärnans integritet relaterar till kognitiv försämring är det sannolikt att sådana hjärnförändringar uttrycker sig i interaktioner mellan funktionella, strukturella och molekylära lager. Denna komplexitet kräver att åldersrelaterad hjärnforskning använder sig av hjärnavbildningstekniker som möjliggör mätning av alla dessa aspekter. Således kombinerades i den här avhandlingen flera olika hjärnavbildningstekniker för att studera den neurologiska grunden för kognitivt åldrande.

Studie I undersökte funktionella konnektivitetsmönster i tre stora funktionella hjärnnätverk (dvs. default mode [DMN], frontoparietal control [FPN], och dorsal attention [DAN] nätverken) under vila och uppgift hos yngre och äldre vuxna. FPN var flexibel i sin anknytning med de andra nätverken genom att vara närmre kopplat till DMN under vila och närmre kopplat till DAN när en kognitiv uppgift genomfördes. Åldersrelaterade skillnader kunde påvisas både under vila och uppgift för FPN men kunde bara påvisas för DMN och DAN under genomförande av uppgift. Sammantaget indikerar resultaten att undersökningar som är genomförda endast under vila inte är tillräckliga för att blottlägga den mänskliga hjärnans hela funktionella nätverk.

Studie II identifierade järn som en potentiell orsak till åldersrelaterade skillnader i hjärnans funktionella kopplingar. Högre nivåer av järn i striatum var associerat med lägre inneboende funktionell konnektivitet i caudate och putamen. Funktionell konnektivitet inom putamen var också associerat med motorisk förmåga, vilket visar att järnrelaterade aspekter av konnektivitet är beteendemässigt betydelsefulla.

Studie III utforskade förhållandet mellan funktionell och strukturell konnektivitet och visade att ökad homotopisk funktionell konnektivitet i den prefrontala loben var associerad med värre mikrostrukturell degeneration av corpus callosum, samt förvärrade försämringen i arbetsminnesförmåga. Däremot, givet att kopplingen mellan funktion och struktur var svag, indikerar resultaten att homotopisk funktionell konnektivitet kan vara motståndskraftig gentemot förändringar i de strukturella hjärnbanornas integritet.

Studie IV fann att dopamin och järn i putamen var positivt associerade men fram till medelåldern. Tillsammans med det faktum att dopamin kräver järn för att syntetiseras indikerar resultaten att mer järn är associerat med högre dopaminergisk aktivitet för individer utan ett övermått av järnackumulering. Högre järnackumulering i putamen var också associerad med bättre mental hastighet.

Sammantaget visar studierna att funktionell konnektivitet påverkas av olika mentala tillstånd, vitsubstansförändringar och molekylära förändringar, där de senare dessutom interagerade med varandra. Dessa olika aspekter är associerade med kognitiv förmåga och interagerar med varandra, vilket indikerar att kognitiv försämring är relaterat till en mängd olika förändringar i hjärnans integritet och att åldersrelaterade förändringar i den mänskliga hjärnan är komplexa och mångfasetterade.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original papers, which are referred to in the text by their roman numerals.

I. **Avelar-Pereira, B.**, Bäckman, L., Wåhlin, A., Nyberg, L., & Salami, A. (2017). Age-related differences in dynamic interactions among default mode, frontoparietal control, and dorsal attention networks during resting-state and interference resolution. *Frontiers in Aging Neuroscience, 9*, 152.

II. Salami, A.*, **Avelar-Pereira, B.***, Garzón, B., Sitnikov, R., & Kalpouzos, G. (2018). Functional coherence of striatal resting-state networks is modulated by striatal iron content. *NeuroImage, 183*, 495-503.

* These authors contributed equally to this work

III. **Avelar-Pereira, B.**, Bäckman, L., Wåhlin, A., Nyberg, L., & Salami, A. Increased functional homotopy of the prefrontal cortex is associated with corpus callosum degeneration and memory decline. *Under review*.

IV. **Avelar-Pereira, B.**, Johansson, J., Kalpouzos, G., Axelsson, J., Nyberg, L., Bäckman, L., & Salami, A. The association between DA D1 receptor availability and striatal iron content across the adult life span. *Manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

AD	Axial diffusivity
BOLD	Blood-oxygen-level-dependent
BP	Binding potential
CC	Corpus callosum
DA	Dopamine
DAN	Dorsal attention network
DARTEL	Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra
DMN	Default mode network
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging
FPN	Frontoparietal control network
FWHM	Full-width at half-maximum
GM	Grey matter
IC	Independent component
ICA	Independent component analysis
MD	Mean diffusivity
MDL	Minimum description length criteria
meGRE	Multi-echo gradient-recalled echo
MNI	Montreal Neurological Institute
MSIT	Multi-source interference task
PET	Positron emission tomography
PFC	Prefrontal cortex
QSM	Quantitative susceptibility mapping
RD	Radial diffusivity
ROI	Region-of-interest
RSN	Resting-state network
SPM	Statistical Parametric Mapping
WM	White matter

1 INTRODUCTION

In the last century, advances in medicine, law, and technology have resulted in major improvements in public health, human rights, and education. The demographic shifts associated with these changes are, arguably, some of humankind's greatest achievements. However, they are also accompanied by major societal challenges. Life expectancy, for instance, is progressively increasing. The proportion of elderly people worldwide was 9.2% in 1990, rose to 11.7% in 2013, and is expected to reach 21.1% in 2050, constituting a total of over 2 billion older people (United Nations, 2013; World Health Organization, 2015). Aging is the biggest risk factor for many disorders characterized by cognitive deficits (e.g., memory problems), such as Alzheimer's disease. Still, cognitive problems are associated with aging even in otherwise healthy individuals. Although there is pervasive evidence linking age-related brain alterations to cognitive deficits, the way in which cognitive changes in aging map onto brain changes remains unclear. There is a need of multimodal imaging work to delineate how the brain relates to cognitive impairment, given that different brain parameters are likely to be correlated with each other.

The goal of this thesis is to provide a modest contribution to the understanding of the neural basis of cognitive aging and serve as a step for future development of intervention programs and better diagnostic tools (e.g., biological disease markers). This introduction is divided into two main sections. First, I will elaborate on the concept of cognitive aging. Second, I will summarize the changes that happen in the brain as we grow older and emphasize those investigated in this thesis: **functional connectivity** (FC), **structural connectivity**, **iron** load, and **dopamine**. As I go through each of these brain parameters, I will give a brief overview of related literature and link them to each of the four empirical studies on which this doctoral project is based.

Cognitive aging

Cognition involves a myriad of processes necessary for everyday functioning. These include, but are not limited to, paying attention and understanding someone's speech, making sense of space and time, and different types of memory processes – from memorizing a set of numbers to the accumulation of memories that, collectively, make up one's personal identity. As we age, however, our capacity to adequately use many of these abilities declines (Harada, Natelson Love, & Triebel, 2013). This is the case for memory, perceptual speed, and reasoning (Cabeza, Nyberg, & Park, 2016; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; Salthouse, 1996). Although cognitive change is a normal part of the aging process, we do not all age in the same way (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). There are large inter-individual differences in both onset (start) and rate (steepness) of

cognitive decline. This is illustrated in Figure 1, where individuals have different levels of performance at 20, but also different patterns of memory deterioration. If we focus on the mean, displayed in bold, memory remains stable till the age of 60, after which it starts declining. This process is called **cognitive aging**.

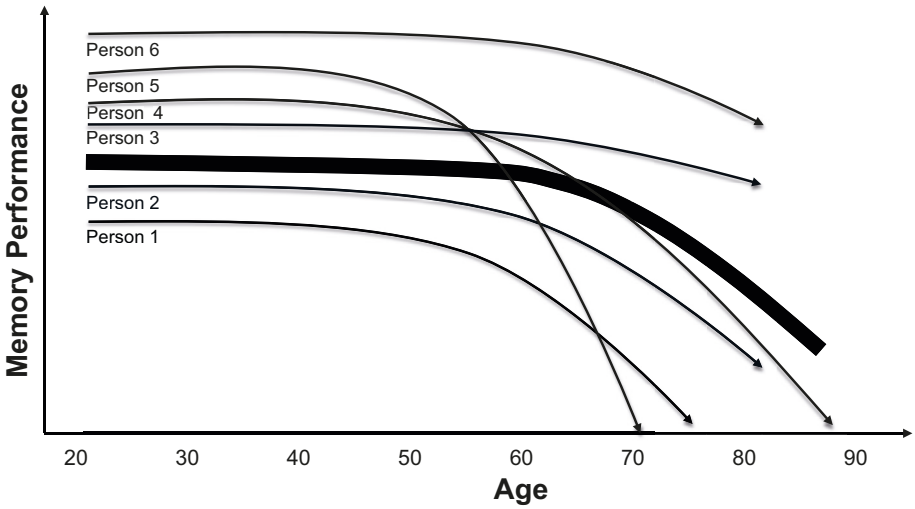

Figure 1. *Graphical illustration of longitudinal changes in memory across the lifespan.*

The above-mentioned estimate of average cognitive decline starting at 60 years old is based on longitudinal work (Rönnlund et al., 2005), but studies investigating cognitive aging make use of a variety of designs. These can be longitudinal, but also cross-sectional, or a mixture of both (Baltes, 1968).

In cross-sectional studies, researchers collect data from subjects who participate in the study only once. A simple example would be the following: memory performance scores are collected from a group of individuals between the ages of 25 and 30 and from another group between 60 and 65 years old. After controlling for possible covariates, any statistical difference in performance between the two groups is considered to be age related. Cross-sectional studies *can* give good approximations of real cognitive decline, but this is not always the case. It is possible that whatever difference found between the groups is not a reflection of real cognitive change but rather a reflection of something we were unable to (or cannot) account for. The two groups mentioned in this example grew up in very different social environments. Poverty is now lower and literacy is higher, and this has had a positive effect in combating socioeconomic inequalities and improving educational attainment and public health. As a consequence, individuals who are now in their 20s are privileged in ways their grandparents were not: they are more

educated and have better access to healthcare. These phenomena have spillover effects, making it hard to tease apart such confounders from true cognitive changes.

In a longitudinal study, subjects are tested at least twice: all subjects in the previous example would be tested at baseline and, for example, again 2 years later. As such, instead of interpreting differences between groups as (possibly) reflecting age-related changes, we can measure true within-subject change. However, these studies also come with limitations. Cognitive tests should be consistent, but retest effects (i.e., increased scores as a consequence of performing the same tests repeatedly) are an unwanted consequence, as is dropout, which rarely happens at random. Longitudinal studies report a much later onset of decline compared to cross-sectional studies, but this could also partly reflect retest effects or attrition bias. Briefly, attrition bias means that individuals who perform poorly or show stepper cognitive decline are more likely to drop out than those who perform at an average or above-average level. Even when retest effects are taken into account, this can lead to underestimated cognitive change. Hence, despite the fact that longitudinal assessments are generally more reliable, there is disagreement regarding the precise onset of age-related cognitive decline (Rönnlund et al., 2005; Salthouse, 2009).

This thesis includes both cross-sectional (study I, II, and IV) and longitudinal (study III) designs and deals with behavioral domains known to decline in aging (e.g., interference resolution, motor performance, working memory, and processing speed). Thus, abilities reported to be resilient or even improve with aging, like vocabulary and general knowledge (Bäckman & Nilsson, 1996), are not investigated. The different tasks employed and underlying cognitive processes will be described in detail in the methods section. Importantly, as I have shown, this research comes with several caveats given the difficulty in identifying the average onset and trajectory of decline. This is primarily due to inter-individual differences, methodological limitations, and the fact that different domains might show differential patterns of decline.

Brain aging

The central nervous system is composed of two types of tissues: **grey** and **white matter** (Figure 2). Grey matter (GM), as the name suggests, is greyish in color and composed of cell bodies, dendrites, and axon terminals. When mentioning *brain regions*, we are specifically referring to GM, where synapses are located. White matter (WM), on the other hand, is composed of axons that connect different GM regions and carry electrical signals. These long filaments are covered in a myelin sheathing, which is what gives them their white color. Generally speaking, one can use a map as an analogy to think about the brain, where cities represent GM and the highways connecting them represent WM.

Functional brain networks consist of two or more GM regions, which can also be structurally connected via WM pathways. However, it is important to note that the existence of a direct structural path is not a prerequisite for a functional network. Each network includes brain regions that typically work together, meaning that they are highly correlated and respond to the same stimuli. Since they were first identified when subjects were resting in the scanner and there was no explicit task involved, they are commonly known as **resting-state networks** (RSNs). In this thesis, I investigated how different RSNs are recruited during rest and task in relation to age (study I) and how the integrity of the pathways connecting different regions relates to functional changes and cognition (study III).

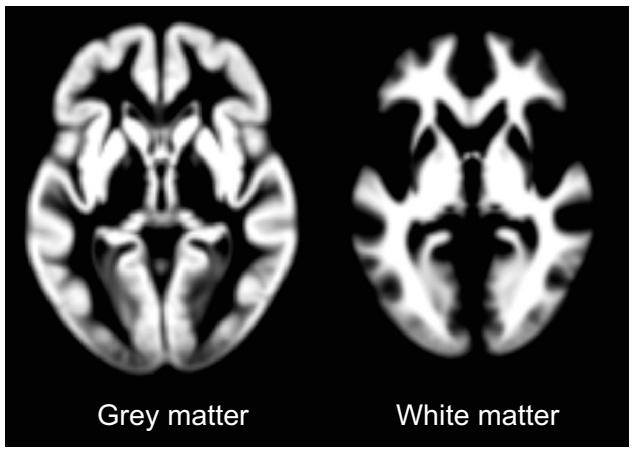

Figure 2. *Magnetic resonance imaging (MRI) images of grey and white matter across participants from the Betula project (study III).*

As we age, there are several changes occurring in the brain: the total amount of GM volume decreases (atrophy; Double et al., 1996; Fjell et al., 2009); the ventricles – where cerebrospinal fluid is produced – expand in size (Barron, Jacobs, & Kinkel, 1976); WM integrity declines due to alterations such as the deterioration of the myelin sheathing (Barrick, Charlton, Clark, & Markus, 2010; Burzynska et al., 2010; Madden et al., 2012); there is a decline in the number of cells involved in neurotransmission (Suhara et al., 1991; Volkow et al., 1996; Wang et al., 1998); and the brain undergoes a functional reorganization (Ferreira & Busatto, 2013; Sala-Llonch, Bartrés-Faz, & Junqué, 2015; Tomasi & Volkow, 2012). However, different brain regions are differently susceptible to age-related degeneration and there is also marked within- and between-subject variability in age-related brain change (Fjell et al., 2013; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Storsve et al., 2014). We know that brain aging is linked to age-related cognitive decline but, as we saw in the previous section, the extent and progression of cognitive deficits among older individuals can also be very variable.

The most commonly studied brain alterations in relation to aging include the above-mentioned grey- and white-matter tissues as well as molecular changes – such as amyloid beta deposition (which is involved in Alzheimer's disease) and neurotransmitters (e.g., dopamine). All these factors have been shown to influence RSNs in aging (Marstaller, Williams, Rich, Savage, & Burianová, 2015; Nyberg et al., 2016; Sheline et al., 2010; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). Still, the neurobiological mechanisms underlying individual differences in RSNs remain unclear.

In this thesis, I also investigated two "molecular" sources of age-related alterations in the brain: **iron**, measured by ferritin and hemosiderin (study II and IV), and **dopamine** (study IV). Molecular is within quotation marks because iron is a metal (a chemical element [Fe] where all the atoms share all of the electrons), not a molecule. However, in these studies, the MRI sequences measure ferritin and hemosiderin as proxies for iron, both of which *are* molecules. For simplicity, iron and ferritin will be used interchangeably throughout the thesis[1].

Contributions of neuroimaging to the cognitive neuroscience of aging

Although other imaging modalities (e.g., computed tomography [CT] and positron emission tomography [PET]) had been available for some years, the advent of MRI, which was presented to the public in 1991, resulted in an exponential increase of research on age-related brain changes and concomitant behavioral effects. Recent technological advances in neuroscience and neuroimaging have also made it possible to integrate in vivo structural and functional human brain changes in relation to cognitive decline. Here, I make use of MRI methods, such as functional MRI (fMRI) and diffusion tensor imaging (DTI), as well as PET, to study the functional and structural organization of the brain. The overall thread connecting the projects in the thesis is the use of neuroimaging to address three questions: (1) how different imaging modalities can inform us about the organization of the brain; (2) how this organization is altered in aging and whether this has a bearing on cognition; and (3) possible reasons underlying age-related differences in functional brain organization. In the following section, I will give a brief overview of the brain correlates examined in the thesis, how they were measured, and why they are important to investigate in relation to aging.

[1] Theoretically speaking, all imaging modalities have a molecular basis, but the division into functional (i.e., functional connectivity), structural (i.e., structural connectivity), and molecular (i.e., iron and dopamine) brain correlates of cognitive aging is made in order to separate them according to the brain features that they *reflect*. For instance, even though the MRI sequence measuring structural connectivity captures the diffusion of water molecules (this will be addressed in detail in a later section), it is meant to reflect the integrity of WM fibers in the brain. In comparison, the MRI sequence measuring iron is meant to reflect iron/ferritin concentration. In this view, the former example is not considered a molecular correlate but the latter one is.

Functional connectivity

Initial knowledge about human brain function came from task-related fMRI studies, during which subjects performed a cognitive task (e.g., working memory) while lying in the scanner. This line of research usually involves a subtraction paradigm. Individuals are presented with a given task and a baseline condition, and the bold-oxygen-level-dependent (BOLD) signal, an approximation of neural activity, is tracked during this period. Afterwards, activity during baseline is compared to activity during task performance. Although useful for the understanding of behavior in relation to different brain regions, this technique also suffers from limitations. It is paradigm-dependent, so it might be difficult to extrapolate findings to other paradigms or more naturalistic settings; it shows that certain regions display increased brain activity at the same time, but gives little information about the actual relationship between them; and ignores most of the energy used by the brain (Raichle, 2006). Specifically, studies on brain energy metabolism have shown that the energy consumption of the brain while performing a specific task is considerably smaller (less than 5%) than the energy it regularly employs at rest (over 20%).

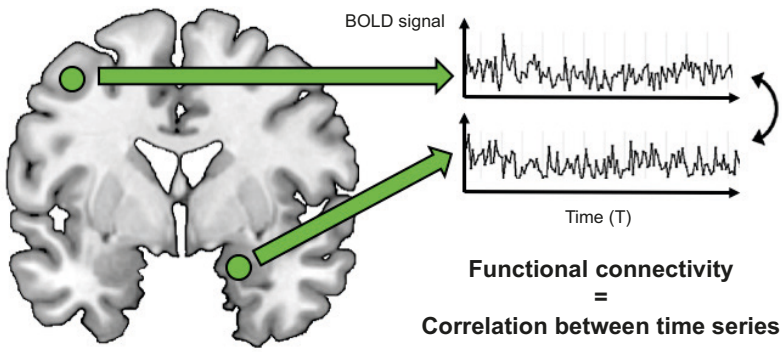

Figure 3. *Schematic representation of functional connectivity between two brain regions.*

Thus, the identification of brain regions associated with specific mental processes can provide valuable information for future research, but also neglects the energy used by the brain when not engaged in a task. Moreover, the brain is not organized in precise categories, where region A is related to process X, but irrelevant for process Y. Our brains are far more dynamic than this. Instead of binary scenarios where a region is engaged versus not engaged in a process, brain activity involves coordinated changes in BOLD signal among different brain regions (Biswal et al., 2010; Fox & Greicius, 2010; Fox & Raichle, 2007; Power et al., 2011; Salami et al., 2010; Salami, Rieckmann, Fischer, & Bäckman, 2014; Wig, 2017). This fact was first noted incidentally in 1995, when researchers instructed subjects in the scanner to lie down and stay still, expecting the BOLD signal to be random. Instead, they found coherence within neuroanatomical systems, with brain regions known to work together showing temporal correlations in BOLD-signal fluctuations (Biswal,

Yetkin, Haughton, & Hyde, 1995; Shen, 2015). These correlations are what we now call **functional connectivity** (FC; Figure 3).

For example, it was found that time-series in the left motor region were specifically correlated to time-series in the right motor region, even in the absence of a motor task (Biswal et al., 1995). This finding gave rise to a new kind of fMRI, which was coined **resting-state fMRI** (rs-fMRI), the name referring to the fact that subjects were scanned while resting. Since then, several studies have found coherence in resting brain activity, revealing large-scale distributed functional systems (i.e., RSNs; Damoiseaux & Greicius, 2009; Shmuel & Leopold, 2008), including the visual, auditory, **default mode** (DMN), **dorsal attention** (DAN), and **frontoparietal control** (FPN) networks (Buckner, Andrews-Hanna, & Schacter, 2008; Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Raichle et al., 2001; Salami, Pudas, & Nyberg, 2014; Salami, Wåhlin, Kaboodvand, Lundquist, & Nyberg, 2016; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), among others (Figure 4).

RSNs show strong within-network connectivity (i.e., high correlation between brain regions belonging to the same network), have a particular topological signature (i.e., a certain shape) and are present not only at rest, but also during task performance and sleep (Picchioni, Duyn, & Horovitz, 2013). Importantly, they are remarkably rich sources of information regarding brain dynamics; they are relatively stable across individuals (i.e., are present in different people), but also person-specific, such that a given FC profile can be traced back to an individual (Finn et al., 2015; Gordon et al., 2017; Shen et al., 2017).

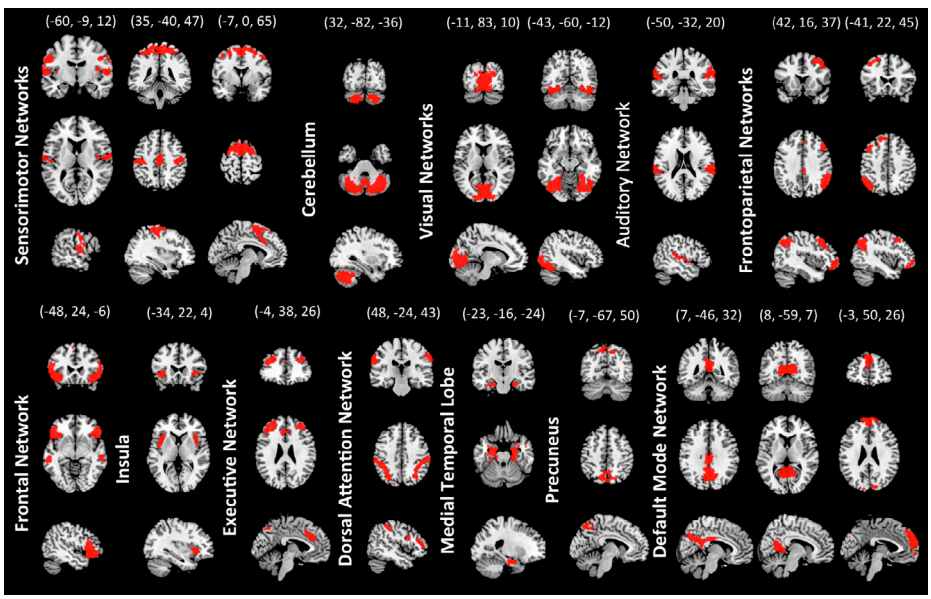

Figure 4. *Example of resting-state networks taken from study II.*

Research shows that RSNs are altered in neurological disorders, such as Alzheimer's and Parkinson's disease, but also in normal aging. Briefly, the brain undergoes a functional reorganization in aging, with changes in the actual architecture of RSNs (Sala-Llonch et al., 2015) and changes in FC strength between different regions (Geerligs, Maurits, Renken, & Lorist, 2014a; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2014b). A common observation is that of functional segregation, where there is a decrease in FC between regions belonging to the same network and an increase in FC between regions belonging to separate networks (i.e., between-network connectivity; Chan, Park, Savalia, Petersen, & Wig, 2014). Still, functional reorganization per se tells us very little about whether there are concomitant behavioral changes. A question of interest in cognitive neuroscience is whether such changes can be linked to future or present cognitive deficits. A better understanding of how RSNs change with aging and the extent to which these changes are static (e.g., present during different cognitive states) or dynamic (e.g., change according to cognitive demands) will help in characterizing and linking them to age-related cognitive deficits.

Resting-state vs. task

The DMN is likely the most well studied RSN and famously known for being deactivated during external goal-oriented cognitive tasks (Buckner et al., 2008; Raichle et al., 2001). Importantly, it is also active during unconstrained cognition, such as mind wandering and rest, as well as during goal-directed cognition, if *internally* focused (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Spreng & Schacter, 2012; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). The FPN and DAN are part of what is traditionally called the "task-positive" network (TPN; Fox et al., 2005). This term is perhaps a misnomer, given that we now know that any network can be task positive, as this is more dependent on context than an intrinsic network characteristic. The name reflects initial research, which pointed to a functional organization where the DMN was only engaged during rest and other networks, such as the FPN and DAN, were engaged during specific cognitively-demanding tasks.

FC among these networks (e.g., how much they communicate with each other) is crucially important for healthy brain dynamics. However, this cross-talk can vary across cognitive states. For example, studies have shown that the DMN has negative connectivity (i.e., is anticorrelated) with the TPN (i.e., DAN) at rest (Fox et al., 2005) and that this negative connectivity increases during task performance (Fornito, Harrison, Zalesky, & Simons, 2012). Other studies show that the DMN has positive connectivity with the TPN (i.e., FPN) during rest and internally-focused tasks (Spreng & Schacter, 2012; Spreng et al., 2010). This might sound difficult to reconcile, but it could mean that the way in which (and how much) these networks communicate varies based on the underlying cognitive state (e.g., on whether some-

one is mind wandering or performing a working memory task). A study by Spreng and colleagues (2010), where subjects had to perform an autobiographical and a visuospatial planning task, indicated that, during autobiographical planning, the FPN was more functionally connected to the DMN. However, during visuospatial planning, the FPN was more functionally connected to the DAN. These results suggest that the FPN increases its connectivity with the DMN, when an *internally* goal-directed cognitive task is involved; and with the DAN, when an *externally* goal-directed cognitive task is involved. The question is whether this pattern is generalizable to other cognitive states, including rest. Similar to autobiographical planning, resting-state also has a self-referential component; it is during this state that people tend to mind wander about their past and future. If the model holds, during rest, the FPN should also be more connected to the DMN and less so to the DAN. During a different, but still externally-focused task, the FPN should be more connected to the DAN.

Studies have also shown that FC between these three networks is disrupted in aging (Geerligs et al., 2014b; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Grady, Sarraf, Saverino, & Campbell, 2016; Salami et al., 2016; Salami et al., 2014). Research on this topic can be divided into two, not mutually exclusive, categories. Some report that the brains of older adults have difficulties suppressing their *within-network* DMN connectivity, and others suggest that the problem is in how the DMN interacts with other networks instead. Still, both these views suggest that older individuals are not able to adequately couple and decouple networks when cognitive demands change (Spreng & Schacter, 2012). Finally, age-related differences in connectivity could vary from rest to task. For instance, a network might need to be engaged in a cognitive process for these differences to become visible. Investigating how FC changes according to age and cognitive state is critical for understanding the predictive power of resting-state fMRI in detecting age-related deficits compared to task-related fMRI.

Functional vs. effective connectivity

I have broadly discussed what FC is and why it is relevant for cognition and in aging. To conclude this section, I will briefly discuss what FC is *not*. By definition, FC reflects a temporal relation between two brain regions, but provides no information about causality. Although it can be tempting to use the terms functional and effective connectivity interchangeably, it is important to remember that the relation that we describe in FC is often measured in terms of correlations. As such, implying that there is a causal relation at play is inaccurate (i.e., "with this, therefore because of this"). Compared to FC, effective connectivity provides a more mechanistic view, by describing the *causal* influence that one neural system (e.g., region A) has on another system (e.g., region B). There are currently several methods to assess effective connectivity, including dynamic causal modelling

(DCM) and Granger causality, but there are still some limitations when it comes to BOLD fMRI data. Importantly, effective connectivity is inferred by estimating the parameters of a predictive dynamic model and is usually constrained by underlying structural connectivity (Friston, 2011; Park & Friston, 2013). Structural connectivity and its relation to function is the next section of this introduction.

Structural connectivity

Structural connectivity is defined as the existence of WM tracts connecting GM regions, and reflects the **structural architecture of the brain**. To study these tracts in the living human brain, we use a non-invasive technique that characterizes water diffusion in nervous-system tissues. This method creates images that are sensitive to the random translational motion of water molecules, a motion formally known as Brownian Motion or Diffusion, and quantifies both directionality and rate of water diffusion within the WM microstructure (Mori & Zhang, 2006). Diffusion is characterized by an ellipsoid represented by a $3 \times 3 \times 3$ matrix (a tensor). As such, the technique is termed Diffusion Tensor Imaging.

Four different measures of WM integrity, which relate to the three main eigenvalues of the tensor, are typically extracted: axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA). AD corresponds to λ_1, and reflects the diffusion rate along the main axis of diffusion, RD is the average of λ_2 and λ_3 and indexes the rate of diffusion in the transverse direction, and MD is the average of λ_1, λ_2, and λ_3, and reflects the average rate of diffusion. FA uses λ_1, λ_2, and λ_3, to quantify the fraction of diffusion that is anisotropic (Figure 5). This means that it will be low in regions where diffusion is not specifically oriented and high in regions where there is a preferred direction of diffusion.

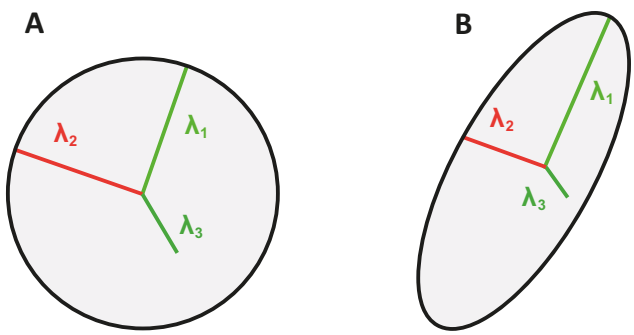

Figure 5. *Representation of diffusion in a given tensor: (A) a cursory look indicates that all eigenvalues (λ_1, λ_2, and λ_3) have similar values and the tensor is isotropic, meaning that there is no preferred diffusion direction; and (B) the eigenvalues have different values, meaning that diffusion goes primarily in one direction (adapted from Tromp, 2015).*

Numerous studies have examined the relationship between WM measures and aging (Barrick et al., 2010; Burzynska et al., 2010; Head et al., 2004), with some also showing associations to cognitive performance (Bender, Prindle, Brandmaier, & Raz, 2016; Madden et al., 2012; Madden, Bennet, & Song, 2009; Persson et al., 2006). Importantly, associations to behavior often show relatively small effect sizes and some studies report non-significant associations as well (Gorbach et al., 2017). It is also more common to find correlations with processing speed (or a measure that is possibly confounded by processing speed) compared to higher-order cognitive functions (Hedden et al., 2014; Laukka et al., 2013; Lövdén et al., 2014; Madden et al., 2004; Nyberg & Salami, 2014; Salami, Eriksson, Nilsson, & Nyberg, 2012).

Still, there is agreement that older individuals show lower FA and higher AD, RD, and MD, compared to younger individuals, although there are reports of increases in FA up to middle age, which challenges the assumption that FA changes linearly across the adult lifespan (Giorgio et al., 2010). Longitudinal studies have also found degeneration in WM tracts in older people in intervals as short as 2 years (Barrick et al., 2010; Charlton, Schiavone, Barrick, Morris, & Markus, 2010; Sexton et al., 2014; Teipel et al., 2010). WM changes in aging seem to follow an anterior-to-posterior gradient, with frontal regions and tracts being affected first and/or being more susceptible to age-related changes (Greenwood, 2000; Pfefferbaum, Adalsteinsson, & Sullivan, 2005). This is in accordance with the so-called "last in, first out" hypothesis, which states that late maturing brain regions or pathways are affected first in aging. However, there are still incongruencies in the literature, perhaps due to factors other than actual WM changes (e.g., cohort effects, measurement error, design and analytical choices, etc.). Such problems are exacerbated by the fact that the majority of studies in the field are cross-sectional in nature, although there is an increase in the number of longitudinal studies investigating these links.

Analytical limitations are likely a large contributor to the lack of reproducibility and incomparable findings among studies, with one of the most cited issues being the prevalence of crossing fibers in the brain (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013). If we go back to the "cities and highways" analogy, we can imagine that, in a given highway, there can be overpasses (i.e., a bridge by which a road passes over another). The same happens in WM pathways: if a given space includes fibers that are bending or intersecting a different fiber group, the method is unable to compute adequate estimates. As it stands, DTI works well at picking out obvious differences in larger fiber bundles between groups, but misses a lot of valuable information due to intersections. There are currently more sophisticated techniques that can address many of these issues, including High Angular Resolution Diffusion Imaging (HARDI; Tuch et al., 2002) or Diffusion Spectrum Imaging (DSI; Wedeen, Hagmann, Tseng, Reese, & Weisskoff, 2005), but these are not commonly used in the field of cognitive neuroscience. There are valid

reasons for this, given that most multimodal studies integrating functional, structural, and molecular brain characteristics include many different MRI sequences, PET, cognitive assessments, and questionnaires. This makes the current protocols already very tiring and time consuming, especially for very young and very old participants. As these techniques require even longer scanning times, it is currently not realistic that we can add 40 minutes to a protocol, unless WM integrity is the main focus of interest.

Relating functional and structural connectivity

FC has been linked to underlying structural connections in the brain (Damoiseaux & Greicius, 2009; Greicius, Supekar, Menon, & Dougherty, 2009; Honey et al., 2009; Skudlarski et al., 2008; Uddin, 2013; van den Heuvel et al., 2009). Specifically, FC seems to reflect, at least partly, the pathways connecting different GM regions. It has been demonstrated that FC is positively associated with structural connectivity strength, but there is also evidence showing FC between brain regions that do not share any direct structural path (Hermundstad et al., 2013; Honey et al., 2009). Moreover, both animal and human work indicates that the level of bilateral FC can remain relatively intact even after complete dissection of the corpus callosum (CC), the major fiber bundle connecting the two hemispheres (O'Reilly et al., 2013; Tyszka, Kennedy, Adolphs, & Paul, 2011). It remains unclear whether and, if so, the extent to which, age-related structural degeneration leads to alterations in FC and associated cognitive decline.

Homotopic connectivity, also called functional homotopy, falls under the umbrella term "functional connectivity". Regular FC refers to the correlation in spontaneous activity between different brain regions, regardless of their specific location, as seen above in Figure 3. As suggested by its name ("homo" means "same", "topic" means "place"), homotopic connectivity refers specifically to the correlation in spontaneous activity between an area in one hemisphere and its equivalent in the other hemisphere (Stark et al., 2008; Zuo et al., 2010b). Research shows that this type of connectivity is generally stronger than connectivity between heterotopic regions (i.e., non-homotopic), or intra-hemispheric connectivity (i.e., connectivity within a hemisphere; Jo, Saad, Gotts, Martin, & Cox, 2012; Shen et al., 2015; Stark et al., 2008). Homotopic connectivity is affected in several conditions, including Alzheimer's disease and mild cognitive impairment (Qiu et al., 2016), depression (Guo et al., 2013), sleep disorders (Zhu et al., 2016), but also in normal aging (Zuo et al., 2010b).

Prior work on homotopic connectivity across the lifespan is based on cross-sectional data. However, as mentioned in the *cognitive aging* section, these estimates can deviate from those found in longitudinal studies. This is also the case in regard to imaging findings. For instance, cross-sectional reports of age-associated frontal over-recruitment are in contrast with those showing longitudinal under-recruitment

in the same regions (Nyberg et al., 2010). Overall, there is a gap in longitudinal work investigating how homotopic connectivity changes over time as well as possible underlying WM changes. Functional homotopy relies primarily on the CC (Aboitiz, 1992), a structure that is divided into genu, body, and splenium, with the genu connecting the most anterior parts and the splenium connecting the most posterior parts of the brain. Studies suggest that, compared to other parts of the CC, the genu might be more vulnerable to age-related degeneration (Head et al., 2004; Madden et al., 2012; Salami et al., 2012). As such, the genu of the CC is often the main target when investigating possible function-structure associations. Finally, although higher homotopic connectivity is often interpreted as reflecting a higher degree of synchronization between right and left hemisphere, whereas lower connectivity is interpreted as reflecting a higher degree of autonomy, it is unclear whether these differences are beneficial or detrimental for cognition. Few studies have investigated this link, precluding definite conclusions about the role of functional homotopy in behavior.

Iron content in the basal ganglia

Compared to the above-mentioned characteristics, iron in relation to the brain and cognition has been less explored. There are several reasons for this omission, one being that only recent advances in MRI have made it possible to non-invasively quantify iron in the human brain. Brain iron comes in two forms: heme iron and **non-heme intracellular iron**. The former is located in the blood and the latter, as the name suggests, is located within cells and most commonly in ferritin proteins. Non-heme iron is of particular importance; it is needed to maintain cellular homeostasis, given that many neurobiological processes are iron-dependent (Daugherty & Raz, 2015; Hare, Ayton, Bush, & Lei, 2013; Mills, Dong, Wang, & Xu, 2010).

In MRI sequences, the assessment of iron content is done through the detection of ferritin and hemosiderin. This is because these molecules are the only types of intracellular iron that exist in large enough concentrations to be identified (Schenck, 1995). Importantly, other types of paramagnetic sources are also present but exist in too small quantities to affect the signal (Haacke et al., 2005). Iron can be quantified with relaxometry (R2*) and quantitative susceptibility mapping (QSM). R2* is one of the most frequently used proxies, but it can overestimate iron concentration due to its sensitivity to myelin. In comparison, QSM can give more robust estimates. Still, both measures are widely validated and reliable markers of brain iron (Deistung et al., 2013; Langkammer et al., 2010). As it can be seen in Figure 6, age-related iron accumulation mostly occurs in the basal ganglia.

Brain iron is almost nonexistent at birth and steadily increases during development until it reaches a plateau in middle age, after which it starts increasing again (Bartzokis et al., 1997; Hallgren & Sourander, 1958; Hect, Daugherty, Hermez,

& Thomason, 2018). There is evidence that, although iron may be beneficial to cognitive functioning during development (Lozoff & Georgieff, 2006), its accumulation in aging typically has the opposite effect leading to, for instance, decreased striatal volume (Daugherty & Raz, 2016). Given that iron is crucial for cellular metabolism, this might explain why, in younger ages, it is associated with better cognitive outcomes. However, with aging, excessive iron is deleterious for brain cells, as it leads to oxidative stress through the Fenton reaction (Winterbourn, 1995; Zecca, Youdim, Riederer, Connor, & Crichton, 2004). Age-associated increases in iron content in the basal ganglia have been previously related to cognitive and motor deficits (Daugherty & Raz, 2015; Daugherty, Haacke, & Raz, 2015). Of note, research also shows that there is iron accumulation in subcortical regions in Parkinson's, Alzheimer's, and Huntington's disease (Connor, Snyder, Beard, Fine, & Mufson, 1992; Zecca et al., 2004). It is unclear why, as we grow older, iron accumulates specifically in the basal ganglia, but it is possibly a consequence of increased permeability of the blood-brain barrier.

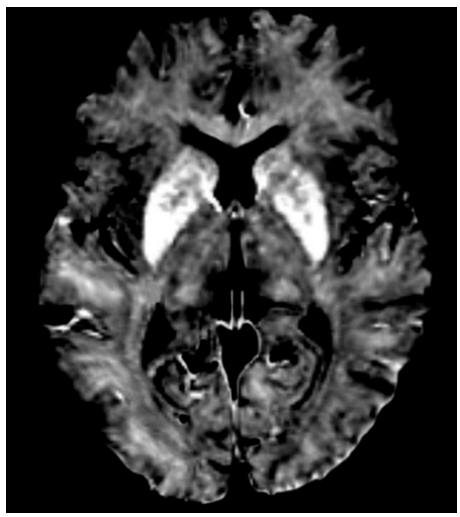

Figure 6. *MRI image of iron concentration (R2*) in the brain from study II; the brightest regions correspond to parts where iron accumulates.*

Brain iron and age-related differences in functional connectivity

A recent study has shown that age-related iron accumulation can be linked to BOLD activity. Older individuals with a higher load of striatal iron showed reduced fronto-striatal activity during a motor-imagery task (Kalpouzos et al., 2017). This result indicates that iron is not only associated with alterations in brain structure, but also alterations in brain function. However, why would striatal iron content

be associated with BOLD signal changes, be it in regard to spontaneous fluctuations or task-related activity? One hypothesis focuses on brain cells where iron accumulation typically takes place. These cells, astrocytes, are partly responsible for many complex brain functions, including regulating blood flow (Connor, Menzies, Martin, & Mufson, 1990; Ward, Zucca, Duyn, Crichton, & Zecca, 2014). There is research suggesting that astrocytes may coordinate changes in blood flow caused by changes in neuronal activity (Figley & Stroman, 2011; Hillman, 2014; Koehler, Roman, & Harder, 2009). As such, it is possible that, when age-related iron accumulation negatively affects the functioning of astrocytes, it also affects the neurovascular coupling we measure in fMRI (Kalpouzos et al., 2017). However, no study has investigated whether FC is also associated with iron content and performance, and if age plays a role in these associations. Extending these findings to resting-state would contribute to better understanding the link between iron load and functional brain integrity.

Dopamine and aging

In this final section, I will discuss the last brain correlate investigated, **dopamine** (DA), and why the relationship between DA and iron content is of interest in the context of this thesis. First, in order for neurons to communicate with each other, they produce action potentials: when an action potential occurs, the cell releases a neurotransmitter into the synaptic cleft, that travels until it reaches the receptors in the receiving neuron (Figure 7). This process, by which chemicals in the brain regulate populations of neurons, is called neurotransmission. Here, the neurotransmitter chosen was DA for many reasons: it deteriorates with advancing adult age and is implicated in neurodegenerative disorders, such as Parkinson's and Huntington's disease (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Kaasinen et al., 2000; Rinne, Lönnberg, & Marjamäki, 1990; Seeman et al., 1987; Suhara et al., 1991). Although produced in the substantia nigra (SN) and ventral tegmental area (VTA), DA is mostly found in the same brain regions where there is age-related accumulation of iron (i.e., striatum, [caudate, putamen and nucleus accumbens]).

To measure DA receptor availability, PET is used. This is a technique where a radioactive compound (also called radiotracer or ligand) is injected into subjects' blood stream and binds to the component of interest. This is done before the start of the imaging session and, as the radiotracer starts decaying, a positron is emitted. When these positrons encounter electrons, they annihilate and emit γ rays, which are then detected by the PET system. Binding potential (BP) can then be calculated by computing the ratio of specific to non-specific binding of the ligand to the receptors.

When DA is released from the presynaptic neuron into the synaptic cleft, it binds to post-synaptic DA receptors. There are essentially two kinds of DA receptor families, D1- (D1 and D5), and D2- (D2, D3, and D4) like receptors, which follow different pathways and have opposite effects. The direct pathway relies on D1 receptors, which are mostly excitatory, and the indirect pathway relies on D2 receptors, which are inhibitory. This means that, whereas the binding of DA to D1 receptors makes it more likely for a neuron to fire, DA binding to D2 receptors does the opposite, making it less likely for a neuron to fire (Keeler, Pretsell, & Robbins, 2014).

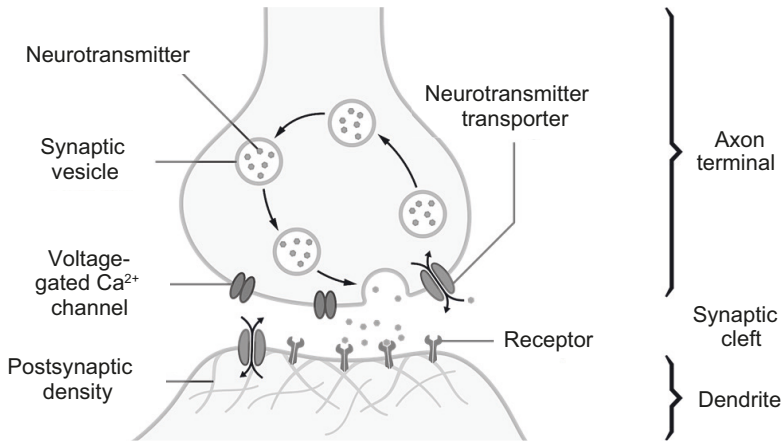

Figure 7. *Neurotransmitter being released into the synaptic cleft (adapted from Splettstoesser, 2015).*

Research has shown DA to be an important modulator of motor and higher-order cognitive functions, such as memory, attention, processing speed, and reward-related behavior (Bäckman et al., 2011; Cervenka, Bäckman, Cselényi, Halldin, & Farde, 2008; Cools & D'Esposito, 2011; Li, Lindenberger, Nyberg, Heekeren, & Bäckman, 2009; Mell et al., 2005; Robertson et al., 2015; Takahashi, 2013). Interestingly, age-related iron accumulation occurs in regions that are rich in DA, with the striatum being a prime example. This suggests that the two processes *might* be interrelated, especially given that DA is synthetized by iron-dependent enzymes. There is evidence that the two measures are correlated based on animal work (Cass et al., 2007; Jellen et al., 2013; Valko et al., 2007), but there have been no human studies exploring these links. Finally, whereas DA reportedly starts to deteriorate during early adulthood, iron remains relatively stable in middle age and only starts to increase again in old age. Given these opposite age-associated patterns, it is also unclear whether age-related differences in DA BP are partly dependent on iron content (and vice versa), and whether this has behavioral implications.

2 AIMS OF THE THESIS

The overall aim of this doctoral project is to contribute to the understanding of the neural mechanisms underlying age-related cognitive alterations. The term "alterations" is used broadly here, given the cross-sectional and longitudinal nature of the datasets included, to refer to both changes and differences in brain function, structure, and molecular properties. This was done via four separate studies:

Study I investigated whether age-related differences in FC were consistent across cognitive states (i.e., rest vs. task), specifically focusing on whether (1) only task-related RSNs were modulated by increasing cognitive demand; (2) the level of modulation predicted performance; and (3) the modulation of different RSNs during a task was age-dependent.

Study II addressed the question of whether iron accumulation in the striatum contributed to age-related differences in RSNs, and whether this had a bearing on motor performance.

Study III focused on changes in homotopic FC over a 5-year period, and whether changes in functional homotopy of the prefrontal cortex (PFC) were related to changes in (1) WM integrity of the genu of the CC; and (2) working memory.

Study IV examined whether there was an association between DA D1 BP and iron content in striatal regions across the adult life span, and whether this link was relevant for processing speed.

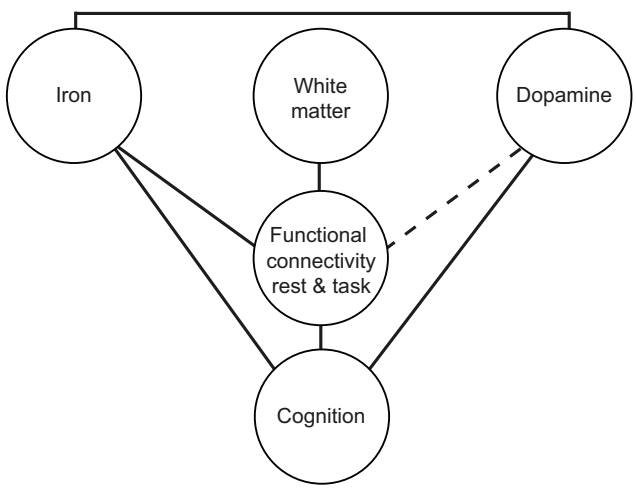

Figure 8. *Schematic representation of the four studies included. Study I: FC during rest and task, and performance; Study II: iron, FC during rest, and performance; Study III: WM, FC during rest, and performance; Study IV: DA, iron, and performance.*

3 MATERIALS AND METHODS

In this section, I will present the study samples included in the thesis. I will then describe the behavioral tasks, provide a broad overview of the neuroimaging analyses used, and summarize the specific methodological procedures followed for each study. For an overall view of the studies, design, brain and behavioral correlates, and main findings, see Table 2 at the end of this chapter.

Study samples

All subjects gave written informed consent and the protocol was approved by the Karolinska Institutet Ethics Committee (study I), Regional Ethical Review Board in Stockholm (study II), or the Regional Ethical Vetting Board at Umeå University (study III and IV), in accordance with the Declaration of Helsinki. Subjects included in the studies were healthy younger and older volunteers recruited in Stockholm (study I and II) or Umeå (study III and IV), Sweden, with no history of past or present neurological illness. Participants' demographic information and global cognition is summarized in Table 1. Surprisingly, study II is the only one where the younger sample had significantly higher education and global cognition scores compared to the older sample.

Briefly, each individual study included a different set of participants. The Emotion and Cognition (Emocog) dataset was used in study I, which, as indicated by its name, is a bigger project with a focus on imaging and emotion in relation to cognition. For the purposes of study I, only subjects who were scanned during resting-state and task performance were included. Study II employed the Iron dataset, which investigates the link between brain iron, other brain characteristics, and cognition. Subjects were scanned during resting-state and during a 3D multi-echo gradient-recalled echo (meGRE) sequence, which measures iron content, and performed a motor task outside the scanner. Participants in study III are part of the Betula project on memory, health, and aging. There have been seven data collection waves so far, but MRI assessment began at the fifth wave (T5). In this study, only participants who underwent resting-state fMRI at T5 and T6 were included. Additionally, participants were also scanned during a DTI sequence and performed a working memory task outside the scanner. Study IV used a subsample of the Dynamic (Dopamine Age Connectome Cognition) dataset, which is part of a large-scale population-based study, where subjects underwent MRI and PET scanning, as well as cognitive testing. D1 BP was measured using the radioligand [^{11}C]SCH23390 (Farde, Halldin, Stone-Elander, & Sedvall, 1987) and a meGRE sequence was acquired during MRI. Overall, the resting-state procedures were identical across studies, lasting from 6 minutes to 6 minutes and 30 seconds. Participants were requested to keep their eyes open and look at a fixation cross.

Table 1. Participants' characteristics.

	Study I		Study II		Study III[a]		Study IV		
	Younger	**Older**	**Younger**	**Older**	**T5 (baseline)**	**T6 (follow-up)**	**Younger**	**Middle-aged**	**Older**
N (Women)	29 (16)	30 (16)	25 (13)	17 (8)	197 (93)		24 (9)	22 (9)	22 (11)
Age (mean ± SD)	29 ± 3.4	68.2 ± 2.6	36.2 ± 4.4	70.1 ± 3.1	59.0 ± 13.1	64.0 ± 13.1	27.5 ± 4.8	43.9 ± 4.4	65.6 ± 7.4
Age range	20–31	65–74	26–42	65–77	25–80	30–85	20–35	36–51	52–78
Education	14.8 ± 2.1	14.4 ± 3.7	2.8 ± 0.4[b]	2.4 ± 0.9*[b]	13.4 ± 4.0		15 ± 2.4	15.6 ± 3.3	14.9 ± 4.8
Global cognition[c]	29.3 ± 0.7	29.0 ± 0.9	28.0 ± 1.6	26.8 ± 1.9*	> 24		29 ± 1.2	28.8 ± 1.1	29.0 ± 1.1

* Age-group differences significant at $p < 0.05$.

[a] The interval between T5 and T6 is approximately 5 years.

[b] Years of education were standardized according to education level (1 corresponds to a lower school certificate, 2 corresponds to a high school diploma, and 3 to a university diploma).

[c] In study I, III, and IV, global cognition was assessed with the Mini Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975). Study II employed the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), where a score of 23 corresponds to a score of 28 on the MMSE (Roalf et al., 2013).

Cognitive assessment

Interference resolution

The multi-source interference task (MSIT; Bush, Shin, Holmes, Rosen, & Vogt, 2003) was used in study I to measure interference resolution. This task consists of three numbers shown at the same time. Participants are required to press a key to indicate which of the numbers is different from the other two. The keys are placed so that they are spatially equivalent to the numbers shown: the first number corresponds to the key on the left, the second to the key in the middle, and the third to the key on the right. In total, the task is comprised of 16 blocks, with alternating control and interference trials. Control trials are fairly easy, because the number that is different always matches its key location and the other two numbers are always 0 (e.g., "020" or "100"). However, on interference trials, the number that differs from the other two never matches its key location, and the other numbers are 1, 2, or 3 (e.g., "212" or "332"). The behavioral outcomes used were accuracy during control and interference. In the MSIT, one is required to ignore information that is not relevant to give an accurate response on each trial. There is well-established evidence indicating that older individuals have difficulty inhibiting this kind of irrelevant information and often perform worse than younger people (Stoltzfus, Hasher, Zacks, Ulivi, & Goldstein, 1993).

Motor ability

Older adults typically show motor deficits (for a review see Seidler et al., 2010). As such, in study II, the Purdue pegboard task (Tiffin & Asher, 1948) was used to compute motor performance scores. This was done outside the scanner. The task primarily measures manual dexterity; however, it is composed of four different sections, with some sections likely reflecting other processes, such as speed and coordination (Strenge, Niederberger, & Seelhorst, 2002). During the first three parts, participants are given 30 seconds to place as many pins as they can using their right hand (part 1), left hand (part 2), and both hands (part 3). In the final part, subjects are given 60 seconds to make assemblies of four different objects but are required to alternate between their right and left hand. The four final outcome measures correspond to the number of pins or assemblies that they were able to place within the stipulated amount of time.

Working memory

Given that working memory declines with aging, several studies have reported age-related alterations in the n-back task (for a meta-analysis see Bopp & Verhaeghen, 2018). In study III, the n-back was performed outside the scanner, where participants were visually presented with a list of 40 words with an interval of 3 seconds between each word. They simply had to reply "yes" if the word presented at any

given moment was the same as the one presented two words before, and "no" if the word was different. The final outcome measure was the sum of all correct responses.

Processing speed

Declining processing speed is among the most typical findings in older individuals (Salthouse, 1996). For study IV, this domain was assessed outside the scanner using a composite score of three separate tasks: a verbal, numerical, and figural comparison task. Participants placed their index fingers over two buttons in a keypad and would press one of the keys to indicate that the two items presented were identical, and the other key to indicate that they were not. The verbal task was composed of 4-letter strings, which were either equal or for which only one letter differed. The same was true for the numerical task, except that this was applied to numbers instead. The figure comparison task was composed of two figures that were either identical or for which only one of the parts differed. Each trial consisted of 40 pairs and participants had one practice and two test trials. The score for each task was computed by dividing the number of correct responses by the total response time. These were then standardized and averaged to form a composite score, in which a higher and lower overall score represented better and worse performance, respectively.

Overview of neuroimaging analyses

Preprocessing of functional connectivity data

Study I, II, and III included FC analyses and, although the samples differed from one study to another, preprocessing steps were carried out in a similar fashion. I will give a summary of these steps and highlight the major differences. In study I and III, Statistical Parametric Mapping Software (SPM12; Wellcome Department Imaging Science, Functional Imaging Laboratory, University College London) was used for data preprocessing. In study II, the data were preprocessed with the Data Processing Assistant for Resting-State fMRI (DPARSFA; Yan & Zang, 2010), a software that relies on SPM preprocessing methods. Briefly, each volume was corrected for within-slice differences in acquisition time, after which images were rigidly aligned to the first volume. This was done in order to correct for head movement. Additionally, in study I, 3dDdespike (which is part of Analysis of Functional Neuroimages [AFNI]) was also carried out. Functional and structural images were aligned using a rigid registration, and T1 images were segmented into GM, WM, and cerebrospinal fluid. This was done at a subject-specific level. A group-specific template was created with Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL), which was then affine aligned to the Montreal Neurological Institute (MNI) template. Importantly, study III included a longitudinal sample and, for that reason, there was an in-between step, where the

creation of a subject-specific template for baseline and follow-up data was computed. These individual templates were used to make a group-specific template. In study I, the data were spatially smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel; in study II and III, this was done with an 8-mm FWHM Gaussian kernel instead. Additionally, the level of anticorrelations between the DMN and DAN was one of the main interests in study I; consequently, no global signal regression was carried out. Finally, the main findings in study II and III include a regression of the Friston 24-motion parameters, whereas, in study I, this was also computed but as a control analysis (Yan et al., 2013).

Independent component analysis

Independent component analysis (ICA) is a multivariate data-driven technique that finds independent sources (also called independent components; ICs) in the fMRI signal, such that ICs are maximally independent. Put simply, ICA assumes that the data are constituted by linear mixtures of independent sources and separates them into statistically independent spatial maps and associated time courses (Allen et al, 2011; Cole, Smith, & Beckmann, 2010; Calhoun & Adali, 2006; Calhoun, Adali, Pearlson, & Pekar, 2001). The "cocktail party problem" is often used as an analogy: person X is at a cocktail party where many other people are speaking simultaneously, and where there is also music and noise. There are multiple recording devices spread throughout the room. Person X's task, after hearing all recordings at the same time, is to separate different sound sources from each other (e.g., the various voices).

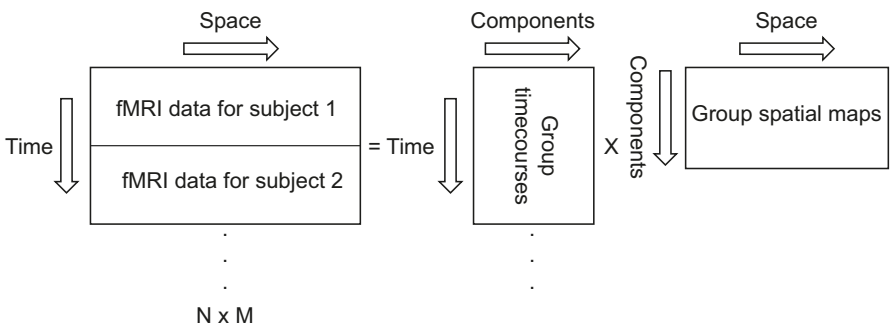

Figure 9. *Overview of a group ICA (adapted from Cole et al., 2010)*

As applied to fMRI data, the goal is to decompose the data matrix N × M, where N corresponds to the number of time points (time) and M to the number of voxels (space), into spatial patterns and time courses (Calhoun & Adali, 2006; Figure 9). A voxel is a cube of brain tissue, representing a 3-D image, and comparable to the 2-D pixels in our televisions (voxel = volumetric pixel). Each voxel represents a million or more brain cells. However, ICA performed at an individual level is not

particularly useful if one aims to do group comparisons. For this purpose, data reduction is performed using principal component analysis (PCA). PCA is a common technique to reduce the high dimensionality present in fMRI data. It does this by identifying principal components: the first component accounts for most of the variance in the data, with the following components accounting for increasingly less variance. The data are first reduced to decrease computational load at the subject-specific level, and the resulting volumes are temporally concatenated. Then PCA is again performed at the group level. Following theses analyses, ICA is applied to the data, and a back-reconstruction and statistical comparisons can be done. In study I and II, ICA was performed using the Infomax algorithm and the optimal number of components was decided by minimum description length criteria (MDL). Back reconstruction was done using a version of dual regression called GICA3 (Erhardt et al., 2011).

Although ICA is what we call "model free", in that it does not rely on a specific modelling approach to detect brain differences (e.g., it does not reflect how well the shape of the hemodynamic response function fits a younger sample compared to an older sample), it does come with assumptions. It assumes, for example, that ICs have non-Gaussian distributions and are statistically independent. Additionally, unlike PCA, which decomposes the data according to eigenvalues, such that the first component explains more variance than the second, ICA is not able to rank order ICs. One can allocate any of the components to the top position, leaving the results unchanged.

Of note, in this section I am specifically addressing *spatial* ICAs, as these were in focus in the present project. It is also possible to determine temporal ICAs, although they are far less commonly used in neuroimaging. The main reason for this being that, most often than not, we have more voxels of interest than we have timepoints. A typical resting-state fMRI scanning session can last between 5 to 10 minutes and, as such, the total number of data points to include in a temporal ICA is extremely limited. This makes the ICA algorithm unstable (Boubela et al., 2013).

Voxel-mirrored homotopic connectivity

Voxel-mirrored homotopic connectivity (VMHC) is a method that computes the temporal correlation coefficients between two voxels with left-right mirrored coordinates (Stark et al., 2008; Zuo et al., 2010b). This is done for every voxel pair across the brain and the values are Fisher z-transformed, after which voxel-wise and region-of-interest (ROI) based analyses can be carried out. VMHC can be used to compute homotopic FC during both rest and task performance. The method itself is fairly simple, but it assumes that the human brain is symmetrical. We know that there can be substantial within- and between-subject anatomical brain variability, so this is not a good approximation of reality; in practice, this

assumption is never met. Spatial smoothing can be applied to counteract the effect of bilateral asymmetry as it improves correspondence between homotopic regions. However, this should be done with caution since it also artificially increases the level of connectivity between the left and right hemispheres. One possible solution to this is repeating VMHC analyses with and without (or with minimal) smoothing to examine how well the main findings in the initial smoothed version match the unsmoothed one. In study III, VMHC was computed and this procedure was followed in order to address such concerns.

Tract-based spatial statistics

Tract-based spatial statistics (TBSS) is a whole-brain automated analytical technique that is distributed as part of the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL). It allows for visualization of group differences in WM. In short, it works by first identifying a registration target (e.g., the most representative subject in the sample) among the available FA images and aligning these images to the target. The images are then affine-aligned to MNI space for ease of interpretation. The second step includes creating a mean of all aligned FA images, after which a skeletonised mean FA is generated. This is done by extracting the medial axis of the WM tracts (i.e., the skeleton) and thinning the previously generated mean image. TBSS considers the center of the tract by identifying the voxel with the highest FA value. The end product is essentially a thin line that represents the center of all tracts common to all subjects in the sample. After this, one can project the images onto the skeleton and perform voxelwise statistics (Smith et al., 2006). This procedure is repeated for AD, RD, and MD. Given that the warps from the nonlinear registration, the skeletonisation, and projection vectors from each subject can be applied to other diffusion weighted images, they do not need to be computed again. Finally, different atlases can be used to extract average FA, AD, RD, and MD, for different tracts. In study III, the John Hopkins University Institute for Computational Medicine DTI (JHU ICM-DTI-81) white-matter labels were used to compute average FA and MD for the CC. Of note, there are different alternatives to the main TBSS pipeline, including a longitudinal pipeline suggested by Engvig et al., (2012). However, in study III, the standard and longitudinal alternatives were highly correlated (FA in the entire skeleton: $r = 0.96$, $p < 0.001$).

R2* and quantitative susceptibility mapping

There are currently several MRI sequences capable of detecting iron content in the brain. In this thesis, R2* (study II) and QSM (study II and IV) were used. R2* is sensitive to other inhomogeneities, such as myelin, which can bias the results. QSM can provide higher specificity because it can distinguish between paramagnetic (e.g., ferritin) and diamagnetic (e.g., myelin) sources. Still, the two measures

are strongly correlated with iron content in post-mortem tissue and can be derived from a meGRE sequence (Langkammer et al., 2010; Langkammer et al., 2012). In both study II and IV, there were eight echo times, from which magnitude and phase images were derived. The magnitude data were used to calculate R2*, and the phase data were used to calculate QSM. R2* (1/T2*) can be estimated by taking advantage of the fact that paramagnetic material, such as iron, has high magnetic susceptibility but also longer transverse relaxion rate (Daugherty & Raz, 2015). For this, a monoexponential model is fit to the square of the signal (Deistung et al., 2013):

$$S^2 = S_0^2 \cdot \exp(-2 \cdot TE \cdot R2^*),$$

here S is the signal magnitude, S_0 is the signal amplitude (with TE = 0), and TE is the echo time. After this computation, average R2* values can be extracted from the relevant regions using the atlas of choice. The second measure, QSM, calculates tissue susceptibility and creates susceptibility distribution maps by inverting the estimated magnetic field. In both studies, this was done with the Morphology Enabled Dipole Inversion (MEDI; Liu et al., 2012; Liu et al., 2011) toolbox. In study II and IV, FreeSurfer ROIs were used to extract estimates in the caudate and putamen (Fischl, 2012). However, it is important to point out that the reference tissue used in each study was different (a ROI in the corticospinal tract in study II, and the cerebrospinal fluid in study IV).

Binding potential

The basics of PET imaging were given in the introduction. Briefly, PET can be used to calculate BP, which is defined as the ratio of bound radioligand concentration to free radioligand concentration, B_{max}/K_d. BP will be proportional to B_{max} if K_d is constant. In study IV, BP of [^{11}C]SCH23390 to D1 receptors was calculated with a simplified reference tissue model (SRTM; Lammertsma & Hume, 1996). FreeSurfer-based ROI analyses were conducted in order to extract time-activity curves (TAC; radiation as a function of time), and the SRTM was fit to the TAC. This was done for the caudate and putamen, but also for the cerebellum, which was chosen as the reference region given that it has negligible expression of D1 receptors. The Desikan-Killiany brain atlas (Desikan et al., 2006) was mapped to individual space by matching structural images with the atlas coordinates.

Analyses in study I

ICA was applied to the functional data using the group ICA fMRI toolbox (GIFT vs2.0a; Allen et al., 2011; Calhoun et al., 2001). This was done first for the resting-state data, in which a total of 21 ICs were identified. A constrained ICA, based on the resting-state results, was applied to the task data. Fischer's z-transformed

Pearson correlation coefficients were used to calculate FC between the networks of interest, during rest and task performance. Younger and older individuals were compared using a 3 (connectivity) by 2 (state) by 2 (age group) repeated-measures analysis of variance (ANOVA). When necessary, these were followed by post hoc t-tests with Bonferroni correction for multiple comparisons. To investigate links to performance, correlations between change in connectivity (rest – task) and accuracy in the task (control – interference) were computed for each network pair. All analyses were controlled for age. Additional statistical analyses were carried out in regard to task-relatedness, to investigate the level to which each of the networks was involved during the MSIT.

Analyses in study II

Similarly, ICA was performed on the resting-state data; a total of 30 ICs were identified, and 20 were deemed representative of RSNs. After this, within-network connectivity measures were computed. Briefly, since each IC includes both a spatial map and associated time courses, a measure based on each of these features was calculated. The intensities in each IC's spatial map were used to compute a voxelwise strength measure, and the time courses were used to compute an average power spectrum (i.e., coherence). A multivariate analysis of covariance (MANCOVA) was then conducted in an exploratory fashion, using the above-mentioned connectivity measures for all networks as dependent variables, and age, iron content (and age × iron content), and sex as covariates. Significant findings pointed to power spectrum in the caudate and putamen networks. As such, correlation coefficients between iron and coherence in these two networks were calculated. After this, between-network measures were computed as well: specifically, a measure of degree centrality and a measure of connectivity strength. Correlations between striatal iron content and these two variables were carried out. A similar procedure was followed to investigate the link between coherence in the caudate and putamen and the Purdue pegboard task. These analyses were computed for each group and across the sample. All analyses were controlled for age and sex.

Analyses in study III

VMHC was performed for baseline (T5) and follow-up (T6) data as described in this chapter. These images were then subtracted (T5 – T6) and one-sample t-tests were computed to investigate change in homotopic connectivity over time. After exploring general patterns in connectivity change, paired t-tests and linear-mixed effects (LME) models in PFC homotopic connectivity in relation to age were performed. Next, the associations between functional and structural connectivity were examined. Given that the Betula protocol involves three different diffusion acquisitions, the data were first concatenated in time, followed by standard

preprocessing steps: eddy-current correction, reorientation of the b-matrix, brain extraction (b = 0), and tensor fitting. FA and MD in the genu were extracted and paired t-tests, followed by generalized additive mixed models (GAMM; Wood, 2006), were conducted. Finally, multiple regressions with change in FA or MD and change in connectivity were carried out. The same procedure was followed for working memory. These analyses were controlled for age.

Analyses in study IV

As mentioned in the previous section, QSM was computed with the MEDI toolbox (Liu et al., 2011) and BP was calculated using a SRTM. BP and iron content in the bilateral caudate and putamen were taken as measures of interest. Subjects were allocated into one of three age groups using a tercile split to guarantee that the groups would be as equal in size as possible. ANOVAs were carried out in order to investigate whether the groups differed in processing speed, DA BP, and iron content. Next, associations between DA and iron in the caudate and putamen were calculated for each group, after which young and middle-aged as well as middle-aged and older subjects were pooled together. After this, associations to processing speed were also explored. All analyses were controlled for age.

Table 2. Overview of the studies.

Study	Dataset	Design	Brain correlates	Behavioral measure	Main findings
Study I	Emocog	Cross-sectional	- Functional connectivity during resting-state - Functional connectivity during task performance	Interference resolution	- Age-related differences in connectivity between the FPN and DMN or DAN are stable across states. - Age-related differences in connectivity between the DMN and DAN vary depending on state. - The ability to shut down the DMN and engage the DAN is associated with cognitive performance in the MSIT.
Study II	Iron	Cross-sectional	- Functional connectivity during resting-state - Iron content	Motor performance	- Higher iron content is linked to lower within-network connectivity in the caudate and putamen. - Iron modulates between-network connectivity of the putamen to the rest of the brain. - Within-network connectivity of the putamen is linked to motor performance.
Study III	Betula	Longitudinal	- Functional connectivity during resting-state - White-matter integrity	Working memory	- There is regional variability in homotopic connectivity change over 5 years; increased connectivity is more prevalent in frontal and subcortical regions. - In the PFC, increased homotopic connectivity is: (1) Partially driven by white-matter degeneration in the genu of the CC; (2) Associated with worse working memory, suggesting that this elevation in connectivity is detrimental for cognition.
Study IV	Dynamic	Cross-sectional	- DA D1 receptor availability - Iron content	Processing speed	- D1 BP and iron content in the putamen are positively associated in middle-aged individuals. This association remains significant when pooling young and middle-aged subjects together. - Iron in the putamen is also associated with processing speed in the middle-aged group.

4 SUMMARY OF EMPIRICAL FINDINGS

Study I: Age-related differences in connectivity during rest and interference

The main results of study I can be summarized as follows: FC between the FPN and DMN decreased from rest to task for both younger ($p < 0.001$) and older participants ($p < 0.001$). This connectivity was also consistently lower in the older group compared to the young during both rest ($p < 0.001$) and task performance ($p = 0.02$). As expected, the reverse was true for connectivity between the FPN and DAN, which increased from rest to task for both groups (younger: $p = 0.003$; older: $p = 0.004$). Of note, the older group showed similar connectivity levels when compared to younger individuals; thus, no age-associated differences in connectivity were found. The degree of anticorrelation between the DMN and DAN increased from rest to task, but only for the young ($p < 0.001$). The younger and older groups did not differ in connectivity during rest ($p = 0.89$), and the older group did not show increased anticorrelation during the MSIT ($p = 0.15$; Figure 10).

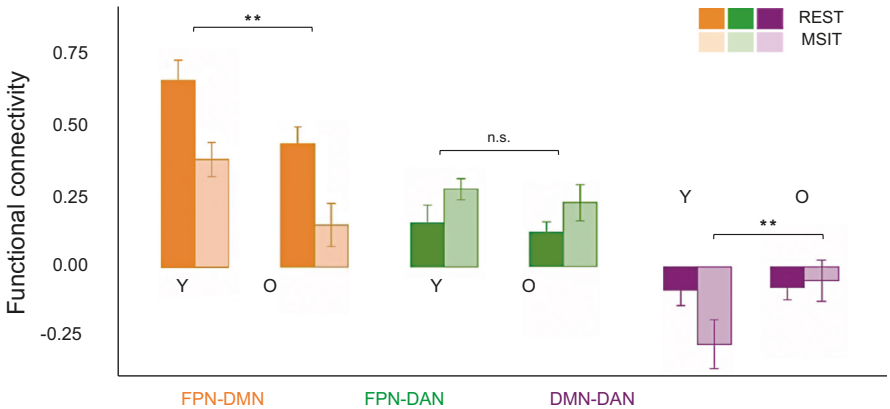

Figure 10. *FC among the DMN, FPN, and DAN during resting-state and interference resolution for younger (Y) and older (O) participants. **p<0.001.*

At a behavioral level, there was an association between accuracy in the MSIT and change in DMN-DAN connectivity ($r = -0.34$, $p = 0.02$). Importantly, the task-relatedness analyses indicated that only the right FPN was positively associated with the task and, as such, the FPN described in the younger vs. older group comparisons is limited to the right hemisphere. However, older individuals also recruited the left FPN from rest to task ($p < 0.001$).

Study II: Resting-state networks and striatal iron content

The multivariate analysis indicated that there were no associations between iron and connectivity strength. However, there was a significant association between iron and coherence for only two networks: the caudate (r = -0.41, p = 0.01; Figure 11A) and putamen (r = -0.32, p = 0.05; Figure 11B). In the caudate, this correlation was also present in the older (r = -0.53, p = 0.04), but not in the younger (r = -0.24, p = 0.27) group. In the putamen, there were no within-group significant correlations (young: p = 0.60; old: p = 0.24).

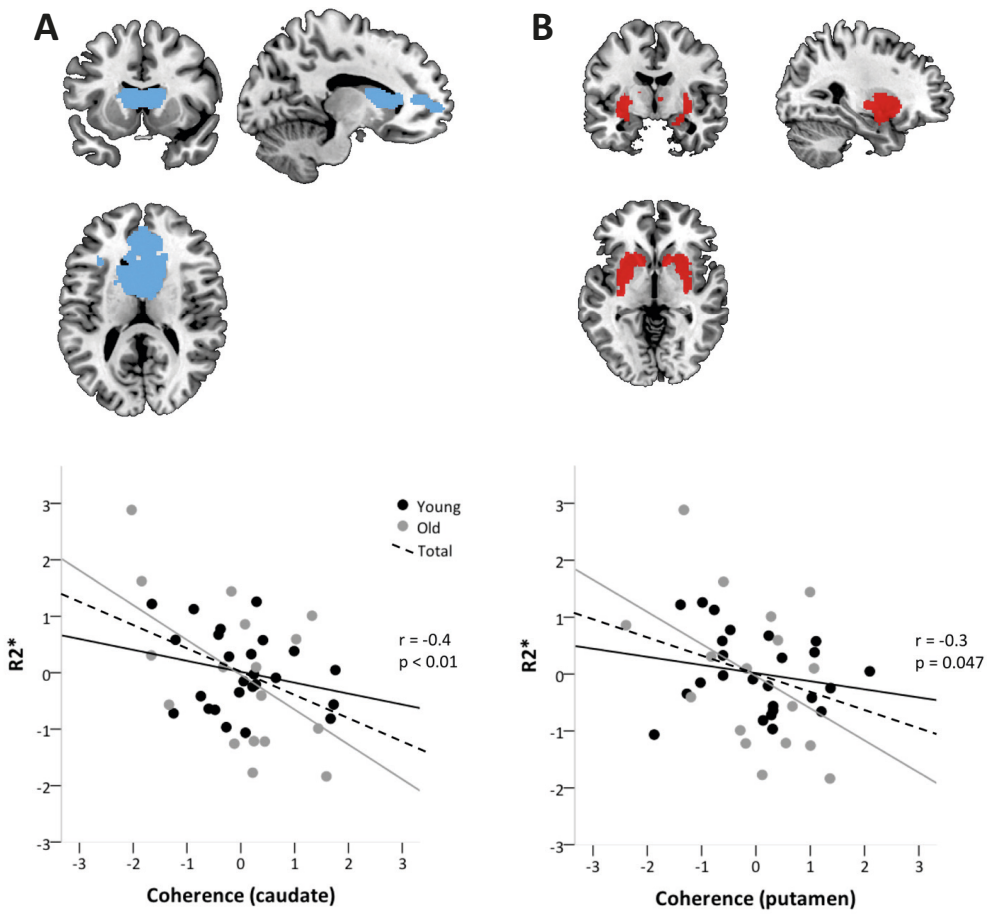

Figure 11. *Negative associations between iron content and coherence in the (A) caudate and (B) putamen RSNs.*

Iron was also negatively correlated with degree centrality in the putamen across the sample ($r = -0.42$, $p = 0.01$; Figure 12A). Again, this link was seen only in the older group (young: $r = -0.30$, $p = 0.12$; old: $r = -0.55$, $p = 0.03$). No between-network associations were found for the caudate at a whole-group level (degree centrality: $p = 0.82$; strength: $p = 0.86$). Finally, across the sample, coherence in the putamen was positively linked to motor performance with the right hand ($r = 0.45$, $p = 0.04$; Figure 12B).

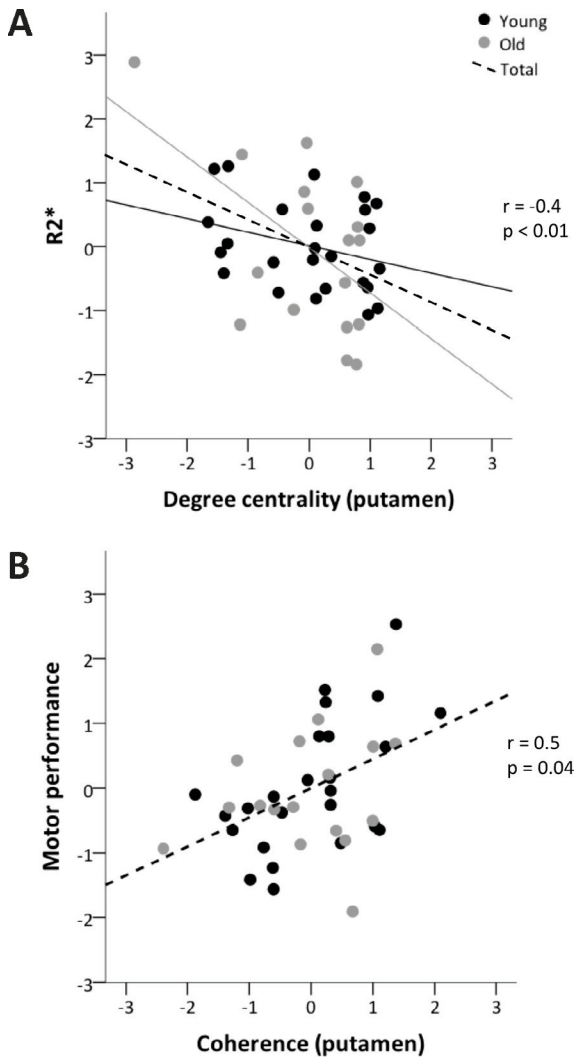

Figure 12. *(A) Negative association between iron content and degree centrality in the putamen; (B) positive association between coherence in the putamen and motor performance.*

Study III: Functional homotopy, white-matter integrity, and working memory

Overall, the results can be summarized in three parts. First, there was variability in homotopic connectivity change, with both increases and decreases over the 5-year interval. Increases were mostly seen in frontal and subcortical regions, whereas decreases were seen in motor and visual regions (Figure 13). Analyses focusing on the PFC showed that homotopic connectivity significantly increased ($\beta = 0.049$, CI: 0.028 to 0.069), however there was no effect of age ($\beta = -0.002$, CI: -0.004 to 0.001) or a time × age interaction ($\beta = 0.001$, CI: -0.001 to 0.002).

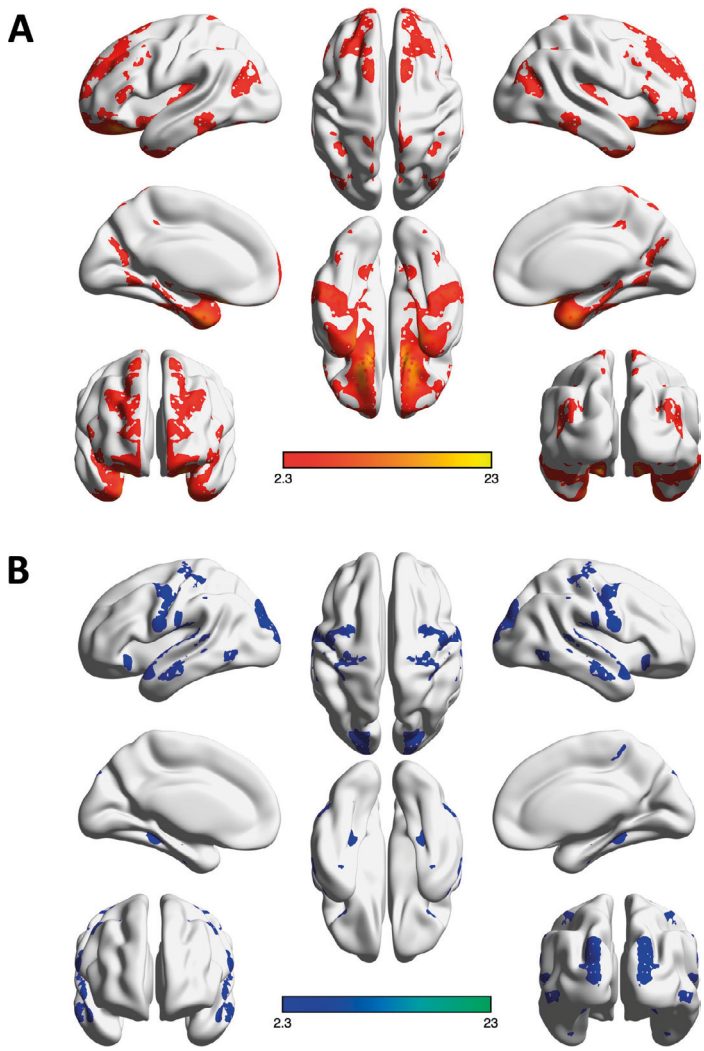

Figure 13. *Brain regions showing (A) increases and (B) decreases in homotopic connectivity.*

Second, the genu of the CC showed a decrease in FA ($p < 0.001$) and an increase in MD ($p = 0.04$; Figure 14). Importantly, there was also a negative association between change in PFC connectivity and change in FA (BA46: peak cluster XYZ = 32 52 24, k = 22, t = 3.21; BA10: peak cluster XYZ = 36 60 12, k = 32, t = 3.95). This means that increased homotopic connectivity of the PFC was associated with decreased WM integrity.

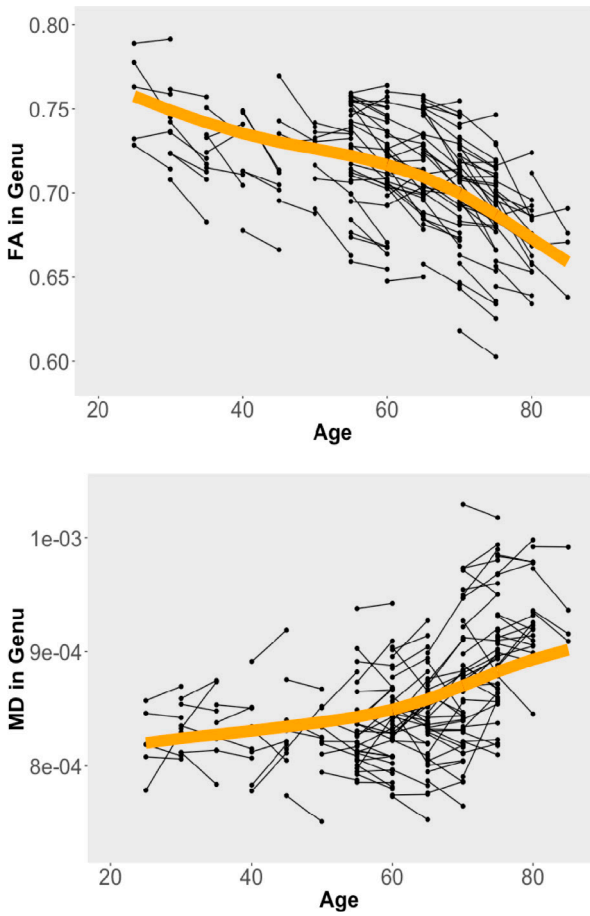

Figure 14. *Individual trajectories in the genu, measured by FA and MD.*

Third, change in homotopic FC of the PFC was negatively associated with change in working memory in three clusters (BA9: peak cluster XYZ = 36 40 44, k = 65, t = 3.49; BA9: peak cluster XYZ = 46 16 52, k = 25, t = 4.62; B10: peak cluster XYZ = 36 62 2, k = 28, t = 3.49; Figure 15), indicating that increased connectivity of the PFC was also linked to exacerbated working memory decline.

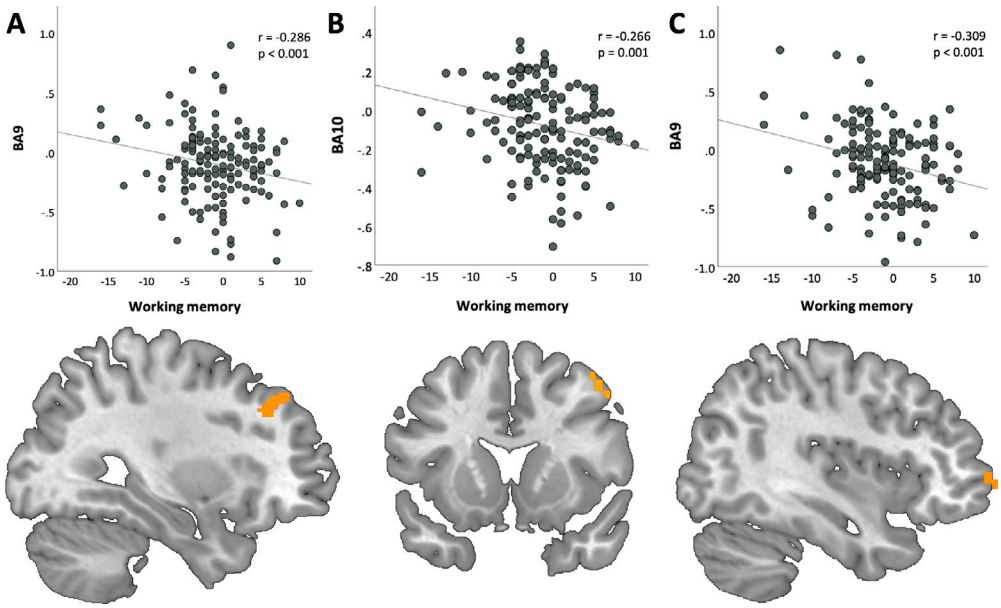

Figure 15. *Scatterplots and brain regions showing an association between homotopic FC and working memory.*

Study IV: The association between dopamine and iron

The results showed that younger subjects had better processing speed scores than the middle-aged ($p = 0.03$) and older ($p = 0.001$) subjects; the middle-aged were also better performers than the old ($p = 0.01$). In both the caudate and putamen, there was a significant difference in BP ($p < 0.001$) and iron content ($p < 0.001$) between the groups. In general, whereas BP gradually decreased from the younger to the older group, iron content gradually increased. There were no significant associations between DA and iron content in the young (caudate: $r = 0.09$, $p = 0.46$; putamen: $r = 0.18$, $p = 0.14$) or in the old (caudate: $r = 0.23$, $p = 0.32$; putamen: $r = 0.02$, $p = 0.95$). In the middle-aged group, there was a positive association between DA and iron in the putamen ($r = 0.47$, $p = 0.03$), but not in the caudate ($r = -0.03$, $p = 0.92$). Importantly, although this association for the young was not significant, it showed a similar trend as the association in the middle-aged group. Moreover, when pooling the two groups together, the correlation between DA and iron remained significant ($r = 0.35$, $p = 0.02$). This was not the case when pooling middle-aged and older subjects together ($r = 0.18$, $p = 0.24$). Finally, higher iron concentration in the putamen was also linked to better processing speed ($r = 0.46$, $p = 0.04$) in the middle-aged group.

5 DISCUSSION

In this thesis, I investigated the neural basis of age-related alterations in cognition. Overall, results show that functional brain architecture is altered in aging and that these alterations are behaviorally meaningful, given that they were associated with cognitive performance in all studies. Possible reasons underlying age-related differences in brain organization, such as structural connectivity, iron load, and dopamine, were also explored.

Briefly, study I investigated FC patterns during rest and task in younger and older adults. Study II and III identified striatal iron and WM integrity as brain characteristics that contribute to altered FC and concomitant motor and cognitive deficits in aging. Finally, study IV examined the relationship between DA and striatal iron across the adult life span. For a detailed discussion of the results in each individual study, see the corresponding papers at the end of this thesis. In the following sections, I will summarize and discuss the main empirical findings, their implications for current and future research, and address methodological considerations and limitations.

Main findings

1 The way in which functional networks communicate with each other *can* (but does not always) vary as a function of cognitive state and age. This means that investigating networks solely during resting-state is not sufficient to uncover the functional connectome of the human brain (**study I**).

2 The frontoparietal network has a flexible connectivity profile, and the degree to which it interacts with the default mode and dorsal attention networks varies depending on task demands. The presence (or absence) of age-related differences is stable from rest to task for connectivity of the frontoparietal network, but state-dependent for connectivity between the default mode and dorsal attention network (**study I**).

3 Functional connectivity can reliably predict performance in a variety of cognitive tasks in both young and older individuals (**study I**, **II**, and **III**).

4 White-matter degeneration in the corpus callosum is directly linked to (homotopic) functional connectivity; however, this connectivity is resilient to subtle changes in the integrity of its structural paths (**study III**).

5 Brain iron is associated with both age-related alterations in functional connectivity and dopamine D1 binding potential (**study II** and **IV**).

The role of resting-state functional connectivity in aging research

Understanding whether changes in FC are present across cognitive states or vary from rest to task (e.g., whether they function in a trait- or state-like manner) is indispensable if resting-state fMRI is meant to stand as a possible diagnostic tool in the future. The fact that it is not paradigm-dependent means that, compared to brain activity studies, it is perhaps easier to extrapolate information to other paradigms. This is likely to result in better generalizability. Additionally, it can be used in populations where long scanning sessions are difficult and perhaps applying a cognitive battery is not an option. As such, resting-state has a special place in both developmental and aging research, making it even more critical to disentangle changes from one state to another in relation to aging. However, the work in the thesis adds to a complicated puzzle where, on the one hand, there is evidence that age differences in FC are not identical across mental states (Geerligs, Rubinov, & Henson, 2015) and, on the other, that such differences are traits of an individual brain (Tavor et al., 2016), and, therefore, rather static, or more easily seen at rest (Grady et al., 2016).

Brain dynamics rely on both network variability and stability. Thus, it is likely that the degrees to which studies find one characteristic to be more relevant compared to another to depend on methodological discrepancies rather than reflect true predominance of one trait over the other. Current advances in neuroimaging allow the study of whole-brain dynamics, a given set of networks or brain regions, or a mixture of the two. Additionally, one can choose to compare connectivity across or within a given mental state, relate it to a variety of measures of individual differences, and to use predefined templates or data-driven ICs, which can include selecting more or less detailed parcellations. These are all examples of decisions made according to the research question, but that can also add to the seemingly incongruent findings mentioned above. Therefore, we need to address these concerns and integrate brain connectivity research that is done at different levels into a far more comprehensive description of the human connectome.

Indeed, a main finding from study I is that resting-state FC does not provide the overall connectivity profile across the entire connectome. Even though there is evidence that resting-state connectivity can predict brain activity at an individual level (Tavor et al., 2016) and that FC patterns can also identify specific individuals (Finn et al., 2015), it is unclear exactly what features of FC are driving these estimates. Understanding where resting-state and task fMRI results concur and where they deviate from one another is essential to make strong conclusions about their predictive value, limitations, and possible clinical applications. If one of the aims of this research is to contribute to the development of intervention programs and diagnostic tools, then there is still a long way to go. Findings of (similarly) altered

connectivity in a variety of disorders preclude conclusions regarding the specificity of resting-fMRI as a valuable biomarker (Castellanos, Di Martino, Craddock, Mehta, & Milham, 2013). The DMN is a prime example of this; dysfunction in within- and/or between-network connectivity of the DMN has been reported in Alzheimer's (Wu et al., 2011), Parkinson's (Lucas-Jiménez et al., 2016), and Huntington's (Quarantelli et al., 2013) disease, but also in autism (Assaf et al., 2010), depression (Bluhm et al., 2009), post-traumatic stress disorder (Lanius et al., 2010), epilepsy (Zhang et al., 2010) and schizophrenia (Chang et al., 2014), among others. These findings are valuable and suggest that the DMN might have a unique role in detecting neurological and psychiatric disorders. However, they also speak volumes to the lack of understanding on how this network specifically relates to any given condition, be it in regard to normal aging, pathophysiological changes, disease progression, or response to intervention (Castellanos et al., 2013).

For the studies in the thesis, there is no available information regarding the exact internal state individuals were in during rest. The question of whether differences in connectivity strength reflect age differences, or whether these are simply confounded by mental state, is an important one. Research shows that people engage in a variety of mental states during resting-state (Andrews-Hanna et al., 2013), and also that older adults have less propensity to mind-wander compared to younger individuals (Maillet et al., 2018). This can affect age-related findings, as it makes the comparison of results somewhat challenging. Currently, functional neuroimaging studies can minimize the effect of many confounders, but it is difficult to adequately control for what people think when they are lying at rest in the MRI scanner. Nonetheless, FC at rest likely reflects two layers of processing: the first, unconstrained cognition, is certainly confounded by an individual's internal state, but the second layer, representing intrinsic connectivity, is less affected by these superficial changes. There are reasons to believe that intrinsic connectivity is an inherent characteristic of the brain, given that it persists when we are sleeping and (to some extent) under anesthesia, and is also present in primates (Nallasamy & Tsao, 2011; Picchioni et al., 2013; Vincent et al., 2007). Brain dynamics at rest and their underlying neurobiological underpinnings are still unclear, but brain organization in segregated networks must reflect, to some extent, maintenance (Wig, 2017). In other words, the brain has most likely found the best way to minimize metabolic expenses, while keeping a connectivity profile that can easily adapt according to the environment and internal demands. Thus, part of what is measured in resting-state fMRI should reflect this nature.

Multimodal imaging and cognitive aging

The main goal of this project was to relate different measures of brain integrity to each other and to investigate whether these have implications for cognition. In order to do this, FC was linked to iron load and WM integrity, and iron was

also linked to DA. Two studies provided evidence that striatal iron concentration is associated with other brain parameters, however this relationship is complex. Iron appears to have a double-edged effect on both brain integrity and cognition. Additionally, there was evidence supporting a link between functional and structural connectivity, but it also seems that the way in which function and structure map onto each other is far from straightforward.

Although the behavioral domains examined are well known to decline in aging, each study included different motor and cognitive measures and, consequently, it is difficult to make direct comparisons among them. Behavioral outcome measures were partly chosen according to the availability in each dataset. Study I used interference resolution, which allowed the investigation of cognitive performance during rest, control, and interference conditions. Because of this, it was found that the FPN was equally engaged during control and interference, whereas the DAN was more engaged during interference trials. If one wishes to argue that the connectivity differences between rest and task found in study I are specifically due to differences in cognitive demands, then the same pattern should also be observed in a task with increasing cognitive load and across different measures of individual differences. Prior research has investigated these issues (Newton, Morgan, Rogers, & Gore, 2011; Salami et al., 2019), but this can be difficult given that a task with increasing load will likely also result in different strategies, which will be associated with different behavioral and neural patterns. Motor performance and processing speed were also chosen as measures of interest. The putamen receives cortical projections from motor areas and, as such, is associated with motor functions, which might have biased the findings in study II and IV (Di Martino et al., 2008; Postuma & Dagher, 2005). Although a link between the caudate and these tasks might still have been expected, this brain region primarily receives projections from associative areas instead. Future studies that include measures of executive functioning are needed in order to make more definite conclusions regarding the effect of iron on motor and executive control. Lastly, study III focused on working memory, given that the region of interest was the PFC and there is consistent work showing that the n-back task recruits this area (Kane & Engle, 2002; Lara & Wallis, 2015). One general conclusion is that FC is reliably associated with performance (study I, II, and III), whereas a direct association between iron and performance was found in one study (study IV), and a link between WM and working memory was not present (study III).

Bilaterality, dedifferentiation, and brain maintenance

Two studies include reports of increased bilateral connectivity. In study I, only the right FPN was linked to task performance. However, the older group also showed increased connectivity between the left FPN and DAN during the task. This is in line with traditional findings of increased bilateral activity and connectivity in older

age (Bäckman et al., 1997; Cabeza, 2002; Cabeza et al., 1997). However, this is a cross-sectional study and, perhaps more importantly, old subjects did not differ from the young in regard to education or MMSE scores, which might imply that this is a highly selected older sample. Moreover, I did not directly test whether subjects who recruited the left FPN to a larger extent performed the task better than those who did not. As such, I cannot make conclusions regarding whether this increase reflects compensation or dedifferentiation (Li & Lindenberger, 1999).

In study III, I tackled this issue from a different perspective, and found that higher homotopic connectivity of the PFC was linked to worse cognitive outcomes. This means that individuals who kept a stable brain connectivity profile from baseline to follow-up (i.e., had smaller increases) performed better in the working memory task. Elevated homotopic connectivity, in this case, could reflect less efficient information transfer. Another account suggests that the CC is responsible for inhibiting connectivity to the contralateral hemisphere. Given the link to WM degeneration, this negative association between functional and structural connectivity might reflect a decrease in the CC's capacity to adequately constrain FC from travelling from one hemisphere to the other (Cook, 1984; Putnam, Wig, Grafton, Kelley, & Gazzaniga, 2008).

Functional connectivity and underlying microstructural changes

FC is present in the absence of structural connectivity and, as such, the extent to which one type of connectivity reflects the other, and how this relates to cognition is currently unknown. In other words, functional networks can be constrained by anatomical networks, but they do not necessarily overlap (Wig, 2017). Findings from study III contribute to ongoing research focused on clarifying these relationships. Importantly, since this is the only longitudinal study in the thesis, it is also the only one that allows for the conclusion that *change* in connectivity is correlated to *change* in a different brain parameter. Even though it seems reasonable to assume that structural changes are the ones leading to FC changes, study III includes two time points and cannot determine the causality of this association.

Although degeneration in the genu of the CC was linked to increased homotopic connectivity of the PFC, this type of connectivity seems resilient to perturbations in its structural paths. Changes in WM integrity were only associated with FC changes in two small clusters in the PFC. As such, the inhibition account mentioned in the previous section might partly explain the longitudinal findings, but it also seems that the brain adapts well to subtle changes in microstructural integrity. The resilience demonstrated by homotopic connectivity fits with previous research where, even after complete dissection of the CC, functional homotopy remained almost intact (O'Reilly et al., 2013; Uddin et al., 2008). This connectivity seems

to have a "contingency plan" in case there is damage to the main structural path by which it travels. Such a plan relies, to a large extent, on the anterior commissure. Nonetheless, this structure is considerably smaller than the CC, which indicates that there must be a number of other smaller tracts (which are necessary, but not sufficient) assisting in the transfer of information across hemispheres (O'Reilly et al., 2013; Risse, LeDoux, Springer, Wilson, & Gazzaniga, 1978; Tovar-Moll et al., 2014).

Importantly, only FA, but not MD, was associated with connectivity. The reasons behind this are unclear; arguably, FA, which has been suggested to relate to fiber integrity, is more sensitive to small changes in WM, than MD (Burzynska et al., 2010; Medina et al., 2006). There are many reasons that can contribute to increased diffusivity, including decreased density of axonal packing within a voxel, fewer axons, change in the extent of myelination, etc. (Chepuri et al., 2002; Madden et al., 2009). Still, linking DTI parameters to specific neurobiological processes or over-interpreting them can be dangerous, given their general lack of specificity and many limitations. However, the fact that neither WM integrity nor working memory were associated with decreased functional homotopy, strengthens the conclusion that increased homotopy is linked to detrimental outcomes.

With regard to the lack of correlation between WM and working memory, there are several not mutually exclusive explanations. First, it is plausible that WM is not a major brain correlate of cognitive decline in normal aging, and that whatever variance it explains can be derived from a different brain measure. The Rotterdam study reported that few age-related differences in FA remained significant after controlling for WM atrophy and hyperintensities (Madden et al., 2009; Vernooij et al., 2008). These are, arguably, also part of normal aging, but, if these findings are generalizable, it is likely that it is not WM integrity per se that is linked to cognitive change, but pathophysiological changes in WM instead. Second, as mentioned in the introduction, WM could be more tightly linked to measures of speed and motor skills than higher-order cognition. Nonetheless, given that DTI can miss much of the brain's structural connectivity due to different fiber orientations within any given voxel, the lack of associations might partly reflect a methodological problem. There is work suggesting that the percentage of crossing fibers in the brain is around 60%; a different method argues that it might be 90% (Jeurissen et al., 2013). Finally, there is also a lot of heterogeneity in the trajectory of WM changes across the lifespan (Mårtensson et al., 2018). For example, FA peaks very early in the fornix (i.e., before the age of 20), but much later in the cingulum bundle (i.e., after the age of 40). Considering this variation, non-significant associations between WM and cognitive variables might largely depend on the sample distribution and specific tracts being investigated.

The double-edged effect of iron

Compared to studies on functional and structural connectivity, there is less literature on the link between striatal iron and brain integrity. Still, age-related iron accumulation in the brain has been shown to lead to decreased striatal volume, lower brain activity, and worse cognition (Daugherty et al., 2015; Daugherty & Raz, 2016; Kalpouzos et al., 2017). The thesis extends these findings to FC at rest and relates brain iron to DA. Higher levels of iron content in the striatum were associated with lower FC in striatal RSNs and worse connectivity to other brain regions, but also with more DA in the putamen. Thus, in the thesis, iron seems be both detrimental (study II) and beneficial (study IV) for the brain. Although in study IV the link between DA and iron was more evident in middle-aged individuals, it remained significant when pooling this group together with the young. In study II, iron was deleterious for FC and this association appeared to be more evident in the older group, though it is difficult to make strong conclusions given that young and old did not differ in degree of correlation. Overall, these findings seem to follow the trajectory of brain iron concentration across the lifespan, which indicates that iron is related to good cognitive outcomes during development and possibly early adulthood, but is deleterious in older age (Daughtery & Raz, 2016; Kalpouzos et al., 2017; Lozoff & Georgieff, 2006; Roskams & Connor, 1994). However, the fact remains that the studies diverge in regard to age-related alterations. One study found a link primarily in older individuals, whereas another found it exclusively in younger subjects. This is surprising and warrants the question of whether the results reflect true differences between age groups or are due to chance. There are many reasons for these inconsistencies, including the fact that subjects in study IV are overall younger, more educated, and perhaps more highly selected (given that they also agreed to PET) than those in study II. If, as it was hypothesized, the negative effects of iron are threshold-dependent, the older sample in study IV might be too young for these effects to be detected, which would explain the lack of negative associations. This is in line with prior research, where the largest detrimental effects of brain iron were seen in subjects above the age of 71 (Ghadery et al., 2015).

Iron accumulation does seem to only become deleterious after reaching a certain threshold. This threshold may differ among people and brain regions, and be differentially expressed in relation to different FC measures. For example, although two measures of within-network connectivity were computed in study II, only one was correlated with iron content. Although speculative, this can be interpreted as reflecting that the correlation between time series is either more sensitive to iron or is affected by it first, whereas alterations in the physical configuration of a network would require more pronounced iron accumulation (Wang et al., 2012; Zuo et al., 2010a). A relation between iron and spontaneous brain activity also finds support in work demonstrating that iron can lead to astrocytic dysfunction, which,

consequently, affects neurovascular coupling and BOLD signaling (Hillman, 2014; Koehler et al., 2009; Ward et al., 2014). FC at rest has been linked to cerebral blood flow supply (Liang, Zou, He, & Yang, 2013), but this link might be weakened in aging. Generally, these findings suggest that brain iron content might explain part of individual variability in RSNs.

DA and iron are both present in high concentrations in the striatum, but follow opposite trajectories across the lifespan, with DA decreases starting on the third decade of life, and iron increasing during development and then again in older age. Iron is necessary for DA synthesis and, as such, the positive association between the two measures can be interpreted from the perspective that, in young and middle-aged adults, where there is no (or negligible) excessive iron load, higher dopaminergic activity requires more iron. Naturally, in older age, this relationship would shift, with excessive iron accumulation leading to cell death. The neurobiological mechanisms underlying this association are unclear, but there is evidence that deterioration of DA neurons in the SN can be avoided by artificially chelating iron so that it cannot participate in oxidative stress (Kaur et al., 2003; Valko et al., 2007).

Findings also suggest that the effect of iron seems more evident in the putamen than in the caudate. Not only was communication between the putamen and other brain regions negatively related to iron, but associations to performance were found exclusively in relation to iron content (study IV) or FC (study II) within the putamen. Though in line with previous research (Ghadery et al., 2015; Manza et al., 2015; Pfefferbaum et al., 2009), it is possible that the results are somewhat biased, given that the performance measures used in both cases were heavily skewed towards motor functioning, which is more commonly associated with the putamen than with the caudate (Middleton & Strick, 2000; Pauli, O'Reilly, Yarkoni, & Wager, 2016; Postuma & Dagher, 2005).

Methodological considerations and limitations

A special focus is given to FC throughout the thesis (study I, II, and III), because it is a relatively easy measure to obtain but also an incredibly rich source of information on brain dynamics. FC does correlate with other brain parameters and some variance that is sometimes attributable to connectivity can disappear after these are taken into account (Marstaller et al., 2015). However, FC seems to clearly have an independent contribution. Still, it is good to remember that this research comes with important methodological limitations. The discussion would not be complete without acknowledging them.

Compared to task-related brain activity studies, FC is particularly sensitive to many parameters that might not be of interest, such as respiration, heart rate, and motion,

which need to be controlled for rather stringently (Birn, Murphy, & Bandettini, 2008; Birn, Smith, Jones, & Bandettini, 2008; Chang et al., 2013; Van Dijk, Sabuncu, & Buckner, 2012). In ICA, for instance, breathing can be especially problematic because its frequency can be close to the signal of interest. Head motion is also a severe concern, particularly in aging research, given that older subjects tend to move more than younger people – which was the case in my studies as well. Presently, there are several ways to address these issues, some of which I mentioned in the methods section, but they remain potential confounding variables. Importantly, in my studies, I was unable to take cerebrovascular factors into account. These can affect the fMRI signal and might confound age-related findings, as there is also a significant change in cerebrovascular physiology with aging (Golestani, Kwinta, Strother, Khatamian, & Chen, 2016). However, in the cases where there was perfusion data available (study I and III), these had less slices and worse temporal resolution than the fMRI data. Hence, they could not be used to separate parts of the signal that were neural-related from those that were not. The lack of perfusion data in study II is problematic for both FC and iron estimates. This is because the MRI signal primarily detects ferritin and hemosiderin (i.e., non-heme iron), but there is also iron in circulating blood that might influence the signal. It is unlikely that the findings of study II were driven by such effects (e.g., if that was the case, the associations should be generalizable to other RSNs and not exclusively to the putamen and caudate). Nonetheless, future studies measuring cerebral blood flow are crucial for research on connectivity in relation to iron.

Another limitation is related to compliance and scanning time. In my studies, subjects were told to keep their eyes open and look at a fixation cross. Yet, I am unable to guarantee compliance to the protocol, given that subjects were not inquired about this after the scanning session and there were no eye-tracking data available. It seems unlikely that they fell asleep, considering that the sessions were short ($\approx$ 6 minutes), and subjects were contacted before and after the sequence while still in the scanner. Moreover, the general pattern of FC also remains similar across different conditions (eyes open vs. eyes closed; Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Bianciardi et al., 2009). Perhaps a more critical limitation is the duration of the scanning sessions. There is work showing that FC reliability plateaus at 12–16 minutes, suggesting that longer scanning sessions might be preferable (Birn et al., 2013). However, it is important to point out that this vastly depends on the goal of the project. If the aim is to discriminate between individuals or to test participants on multiple occasions, longer sessions will allow for better discrimination and validity. In the thesis, I investigated age-related alterations in (average) FC in relation to age. Based on the literature, this connectivity is stable within 5–7 minutes of scanning (Van Dijk et al., 2009).

Three of the studies included in the thesis have limited sample size. In view of recent concerns over reproducibility and statistical power, they await validation in larger samples. Although this is a long-standing issue in science and perhaps one of the most (if not the most) serious methodological concern in psychological sciences and neuroimaging, it has only been amply debated in recent years (Button et al., 2013). Currently, there is ongoing work investigating the association between brain iron and other brain and behavioral parameters in a bigger sample ($N > 200$), which will help clarify the nature of the relations here reported. Moreover, study IV used a subsample of a large-scale population-based study, for which data collection is still ongoing. This means that a significantly larger sample will soon be available. Finally, the sample in study I is from a completed project, however there is published research showing results that concur with the findings reported in this thesis (Salami et al., 2014; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013).

So far, I have summarized more general limitations in FC analyses. One last question, however, is the motivation behind using ICA in study I and II when there is a multitude of methods to choose from. There are many different approaches to analyzing functional networks, each with its own pros and cons. For example, predefined templates can be useful, but they are also more sensitive to small changes in the location of the seed, which can bias a connectivity matrix. Furthermore, any two voxels correlated with a seed are not necessarily correlated with each other. Compared to seed-based approaches, ICA takes into account the relation between all voxels and can be more sensitive to age-related differences (Allen, Erhardt, Wei, Eichele, & Calhoun, 2012). Moreover, unlike general linear models (GLM), ICA does not require an explicit temporal model. This does not mean that ICA comes without limitations: estimating the optimal number of components, for instance, is problematic (Allen et al., 2012).

Different methods have different limitations and advantages, so they complement each other and can also address somewhat different questions and from different perspectives. Although these were not part of the aims of the thesis, FC metrics vary over time and within a given mental state. Hence, it is also of interest to explore dynamic FC using methods such as sliding windows or time-frequency analyses (Hutchison et al., 2013). All connectivity findings reported in the thesis are of FC, meaning that their nature is *descriptive*. No inference about the coupling between two brain regions is made. Investigating causality in relation to the research questions in my studies would require, as mentioned in the introduction, analyses of effective connectivity, which can provide a measure of causality. I primarily compared FC in relation to age and a set of different brain and behavioral parameters and laid out a general blueprint on how these interactions take place and what might influence them. Graph-theory approaches can now be useful to generate additional and more detailed information on the hierarchy, specific organization, and different properties of functional networks.

Concluding remarks

In this thesis, I investigated functional, structural, and molecular brain correlates of cognitive aging. The use of multiple imaging modalities was crucial here, as each provided distinct information about the architecture of brain networks. Study I provided evidence in favor of age-related differences in FC during rest and task, and suggests that some networks have a particularly flexible FC profile compared to others. However, this is likely dependent on the measures of individual differences taken under consideration. Study II and III showed that brain iron and WM integrity are associated with altered FC and cognitive deficits in aging. Study II and IV contributed to existing literature on brain iron in relation to aging, by showing that striatal iron content is associated with FC at rest (study II), and can also be meaningfully linked to DA in humans (study IV).

Importantly, what is referred to as multimodal imaging in this thesis meant, in part, combining data points from separate studies. A true multimodal approach would provide all imaging and cognitive data for all participants. Future studies can address this issue by investigating the link between the measures reported here, but in the same study sample. Moreover, although there are now a number of longitudinal studies, which can help to either validate or contest current cross-sectional findings, not many have more than two measurement points and often involve short intervals. In regard to the association between two variables that change together, at least three time points are necessary to make conclusions about which one changes first. Studies linking multimodal imaging domains should also give particular focus to other factors, such as lifestyle choices, education, and genetics. For example, not much is known about modifiable factors that can help to either slow down or maybe even prevent age-related accumulation of iron. Understanding how and why iron accumulates in the brain with aging might contribute to preserving the integrity of RSNs and promote healthy brain aging. Given the limitations of DTI, continued work on developing more sophisticated ways to measure WM in the human brain in vivo will also result in more robust estimates, which can be used in conjunction with functional imaging research. Although a relationship between iron and DA is reported in the thesis, only D1 receptors were investigated. Future studies should disentangle whether D1 and D2 receptors are differently linked to iron content. Finally, although we can obtain valuable information from static changes between states as it was investigated in this thesis, a full understanding also involves more fine-grained dynamics at different spatial and temporal scales. Brain organization can be studied at multiple levels and taking into account different measures of individual differences. These need to be integrated into a comprehensive description of brain dynamics in healthy and pathological aging.

Though most studies are cross-sectional and cannot inform us about causality, they represent an important contribution to a model of aging where iron is likely to precede structural (and perhaps) functional decline. Still, these relationships are complex. In the thesis, FC was influenced by mental state, WM changes, and molecular properties, with the latter also being interrelated among themselves. Future work should focus on exploring the directionality of these associations, as well as establishing which measures are most sensitive to cognitive change. For instance, prior work has shown that FC mediates the association between DA and cognitive performance (Nyberg et al., 2016), as well as the association between WM and memory impairment (Qiu et al., 2016). The same could be true for iron load. Although the brain parameters investigated in the thesis have multifaceted and likely bidirectional relationships, this would suggest that FC can be consistently linked to all of them and, thus, is likely to reflect a measure of overall brain dysfunction. Understanding which changes in connectivity are specifically linked to changes in these other brain features would then provide specificity and allow researchers to isolate specific brain changes associated with a given set of behavioral symptoms. In this thesis, I hope that I have made a small contribution toward this goal, given that this understanding is also critical for differentiating normal age-related changes in brain integrity and cognition from those that are pathological. Only by doing that, we can hope to detect early signs of pathology and either prevent further brain degeneration or perhaps, one day, even ameliorate it.

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8 APPENDIX

Dissertations from the aging research center and Stockholm Gerontology Research Center, 1991–2019

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly – Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hilleråas Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hilleråas Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly – Risk or protection? Findings from the Kungsholmen project.

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.

Rehnman Jenny. The role of gender in face recognition. (Stockholm University)

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence.

Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.